Post-Cesarean Delivery Analgesia

Jeff Gadsden, MD*, Stuart Hart, MD†, and Alan C. Santos, MD, MPH†

*Department of Anesthesiology, St. Luke's-Roosevelt Hospital Center of Columbia University, New York, New York; †Department of Anesthesiology, Ochsner Clinic Foundation, New Orleans, Louisiana

Post-cesarean delivery pain relief is important. Good pain relief will improve mobility and can reduce the risk of thromboembolic disease, which is increased during pregnancy. Pain may also impair the mother's ability to optimally care for her infant in the immediate postpartum period and may adversely affect early interactions between mother and infant. Pain and anxiety may also reduce the ability of a mother to breast-feed effectively. It is necessary that pain relief be safe and effective, that it not interfere with the mother's ability to move around and care for her infant, and that it result in no adverse neonatal effects in breast-feeding women. The most commonly used modalities are systemic administration of opioids, either by intramuscular injection or IV by patient-controlled analgesia, and neuraxial injection of opioid as part of a regional anesthetic for cesarean delivery. These techniques have specific advantages and disadvantages which will be discussed in this review. In addition, there are new drug applications of potential benefit for the treatment of post-cesarean delivery pain.

(Anesth Analg 2005;101:S62–S69)

The benefits derived from relieving postoperative pain in surgical patients have been summarized elsewhere and also apply to women having a cesarean delivery. However, there are additional compelling reasons to provide adequate pain relief for mothers undergoing cesarean delivery. For instance, risk of thromboembolic disease, which is increased during pregnancy, may be further exacerbated by immobility related to pain during the puerperium. Pain may also impair the mother's ability to optimally care for her infant in the immediate postpartum period and may adversely affect early interactions between mother and infant. Pain and anxiety may also reduce the ability of a mother to breast-feed effectively. This review will focus on commonly used strategies, such as systemically administered analgesics and neuraxial techniques as well as new drug applications, for relieving pain after cesarean delivery.

Systemic Administration

Systemic administration of analgesics, in most cases opioids, is a commonly used modality for immediate post-cesarean delivery pain relief, particularly after general anesthesia. Analgesics may be given by intramuscular (IM) or IV injection. In some women, simple oral administration may be sufficient if bowel function is normal. The advantage of systemically administered analgesics is their ease of administration, low cost, and long history of use in postpartum women. Women receiving systemically administered analgesia usually do not require heightened vigilance for delayed adverse side effects that may occur with neuraxial techniques, although pain relief is less effective.

Intramuscular/Subcutaneous Injection

IM or subcutaneous administration of opioids is the most frequently used modality for post-cesarean delivery pain relief for the aforementioned reasons. However, there are some serious limitations to their use. First, drug administration requires injection, often repeated, which may be uncomfortable for many women. Second, there is large inter-individual variability in opioid pharmacokinetics and drug requirements. For instance, after abdominal surgery, C_{max} (peak concentration) and time to peak concentration varied by almost fivefold in women given meperidine by IM injection (1). There is also little correlation between body weight and blood concentration of meperidine, which is problematic for estimating an effective dose regimen (2). Furthermore, with IM administration, there are peaks and valleys in opioid blood concentration that can affect pain relief and the incidence of side effects (3). At C_{max}, the patient may have

Financial support for preparing this manuscript was provided by an unrestricted educational grant from Endo Pharmaceuticals, Chadds Ford, Pennsylvania.

Accepted for publication June 22, 2005.

Address correspondence and reprint requests to Alan C. Santos, MD, MPH, Department of Anesthesiology, Ochsner Clinic Foundation, 1514 Jefferson Highway, New Orleans, LA 70121. Address electronic mail to obanesdoc@aol.com.

DOI: 10.1213/01.ANE.0000177100.08599.C8

0003-2999/05

effective pain relief but have an increased incidence of unwanted effects, such as somnolence and sedation, whereas at smaller concentrations, pain relief may be inadequate.

In an era of nursing staff shortages, parenterally administered opioids may be inconvenient for the nursing personnel and the patient. This approach requires the patient to call for the nurse to administer the injection. Once the nurse responds to the call, he or she must verify the order (a person with prescribing authority may need to be contacted), sign out the opioid, prepare it, and then return to the patient's bedside to administer the injection. After the injection, pain relief is not immediate. Rather, there is a variable interval required for absorption of the drug from the site of injection and for the drug to reach opioid drug receptors. Furthermore, at the end of every shift, regulations require a full accounting of controlled substance floor stock and use, which consumes staff resources.

Patient-Controlled IV Analgesia

Many limitations encountered with IM administered opioids can be overcome with the use of patient-controlled IV analgesia (IVPCA), which requires that the patient demand a small bolus of opioid administered IV by a device. The device is programmable for the dose administered, a lockout interval, whether a basal infusion of drug is given, and as an added protection, maximum dosages within specified time periods.

The advantage of IVPCA is that it reduces the peaks and valleys in blood drug concentrations and pain relief observed in post-cesarean delivery women, in part by bypassing the patient-nurse-injection loop. Pain relief with IVPCA has been shown to be superior to conventional IM opioids for pain relief in women having had a cesarean delivery (4). For instance, in a comparison of opioids administered by IM, IVPCA, or epidural injection, the number of instances in which women reported being uncomfortable or in pain was least for epidural opioid and largest after IM opioids; the IVPCA was intermediate (4). Women having IVPCA had the highest satisfaction scores despite reporting less complete pain relief than those given epidural morphine (4). However, opioid usage was largest in women having IVPCA, 11 $\pm$ 2.3 morphine equivalents (mg) as compared with 1.0 $\pm$ 0.6 and 3.8 $\pm$ 1.1 morphine equivalents (mg) in the epidural and IM groups, respectively (4). It has been speculated that the reason patient satisfaction is greater with IVPCA as compared with epidural opioid, despite the fact that the latter is more effective, is greater autonomy and control of the woman over her care, something that is important as she balances her needs to care for her infant. On the other hand, the more frequent incidence of pruritus with epidural morphine as compared with IVPCA may have resulted in less maternal satisfaction with the former.

For the most part, meperidine is rarely used for post-cesarean delivery analgesia, particularly if the woman is breast-feeding. Repeated administration of meperidine can result in accumulation of the active metabolite, normeperidine, in breast milk and can reduce scores on the Brazelton Neonatal Behavior Assessment Scale (5).

Whether to administer a background continuous infusion of opioid in addition to demand mode IVPCA is controversial. Patients may not use the demand mode for various reasons, such as fear of addiction, and as a result patients may be in unnecessary pain unless a background infusion is used. Also, a continuous infusion may provide basal analgesia to build upon with demand doses in anticipation of periods associated with more pain, such as with movement or rehabilitation. However, it is possible that a basal infusion may decrease the safety of IVPCA by continuing to administer drug even if the patient is pain free or sedated. Furthermore, use of a basal infusion does not appear to enhance pain relief beyond that afforded by demand IVPCA alone. In one study, 230 women having abdominal hysterectomy were randomized to receive demand mode IVPCA with an added basal infusion of 0.5, 1.0, or 2.0 mg/h of morphine; the control group received demand mode only (6). Administration of a background infusion at any of the morphine doses tested did not improve pain relief beyond demand mode only IVPCA, as measured by visual analog scores. Furthermore, there was no significant difference among groups in the number of demands or the delivered doses per hour. Interestingly, addition of a continuous basal infusion of morphine to demand mode IVPCA did not increase the incidence/severity of bothersome side effects, such as nausea and vomiting, confusion, undue sedation, or pruritus.

The most significant limitations to the use of IVPCA in postpartum women relate to the device itself and patient ability to use it correctly. The latter requires patient education and implies that the patient will understand and follow through with directions required to use demand mode IVPCA effectively. The device itself has an added cost over the use of conventionally administered opioids. In contrast, IVPCA may reduce the work of floor personnel particularly on a busy postoperative floor. Another limitation of IVPCA is that some devices may be cumbersome and women may find it difficult to ambulate and care for their infant. Nonetheless, IVPCA has emerged as a popular modality for post-cesarean delivery pain.

Neuraxial Analgesia

It has been almost 25 yr since neuraxial opioids first underwent rigorous clinical study for use in humans (7). Since that time, neuraxial techniques of providing post-cesarean delivery analgesia have become a logical outgrowth of the increased use of regional anesthesia for the procedure. For instance, a review of the most recent Obstetric Anesthesia Workforce Survey (8) reports a sizeable increase in the use of spinal and epidural over general anesthesia for cesarean delivery from 1979 to 1990. Similarly, data from the United Kingdom show that regional anesthesia is used 94.9% of the time for elective and 86.7% of the time for emergent cesarean delivery (9). Addition of opioid, like morphine, to intrathecal and/or epidurally administered local anesthetic provides an easy and effective means to maintain prolonged postoperative analgesia. Neuraxial techniques may be used for post-cesarean delivery pain relief even in women having general anesthesia, if they so desire, once they are awake.

Mechanism of Action

Opioids administered in the subarachnoid space appear to act principally on mu receptors in the substantia gelatinosa of the dorsal horn by suppressing excitatory neuropeptide release from C fibers (10). The degree of uptake from the cerebrospinal fluid by the dorsal horn is determined primarily by the physicochemical properties of the drug, and in particular, lipid solubility. Lipid-soluble compounds enjoy greater direct diffusion into neural tissue as well as greater delivery to the dorsal horn by spinal segmental arteries. For instance, fentanyl, which is highly lipid soluble, has a relatively rapid uptake into the lipid-rich dorsal horn and, consequently, has a swift onset of action. The large uptake of highly lipid-soluble opioids by the spinal cord results in small cerebrospinal fluid concentrations and a decreased potential for the drug to diffuse to higher spinal levels. For this reason, the analgesic effect of fentanyl is thought to be segmental.

In contrast, morphine is highly ionized and hydrophilic and does not penetrate lipid-rich tissues as well as fentanyl does; it thus lingers in cerebrospinal fluid. Morphine spreads rostrally within cerebrospinal fluid by bulk flow and reached the trigeminal nerve distribution as early as 3 h after intrathecal injection in healthy volunteers (11). This rostral spread of drug may result in delayed respiratory depression manifested by decreased respiratory rate and decreased arterial oxygen saturation. The concern of delayed effects relates to the potential for the woman to be in a less-monitored environment. Duration of action of analgesia is also largely a result of lipid solubility, with hydrophilic drugs such as morphine having a relatively prolonged effect as a result of their slower disappearance from the cerebrospinal fluid and spinal tissues. In contrast, more lipid-soluble opioids, such as meperidine or fentanyl, have a shorter duration, reflecting rapid uptake and elimination from spinal tissues (12). Affinity for the mu receptor is also important in duration of analgesia. For instance, sufentanil, which is considerably more lipid-soluble than fentanyl (their octanol partition coefficients differ by more than twofold), and therefore might be expected to be shorter-acting, has in fact a comparatively prolonged duration. This is thought to result from increased receptor affinity for sufentanil compared with fentanyl. Uptake of opioids into the systemic circulation after intrathecal injection is usually not significant, as the doses typically used in the spinal space are small. This is particularly important to breast-feeding women and is an advantage of neuraxial modes of post-cesarean delivery pain relief as compared with the larger doses of opioids required systemically.

The mechanism of action after epidural injection is somewhat more complex, owing to the presence of a dural barrier, the role played by epidural fat as a drug depot, and the vastly increased vascularity of the epidural compartment during pregnancy. When a hydrophilic drug, such as morphine, is injected, it moves slowly across the arachnoid granulations (10), and speed of onset of analgesia is correspondingly slow. Eventually, a large concentration of ionized morphine accumulates in the cerebrospinal fluid that not only leads to rostral diffusion but also a long duration of analgesia. Vascular absorption of morphine by the epidural venous plexus is relatively rapid, with plasma C_{max} within 15 min (13). However, analgesic effect correlates poorly with plasma levels (14) because there is a predominant spinal mechanism of analgesia after epidural administration of the drug. In one study, blood levels of morphine were similar in volunteers 1 h after IV and epidural administration of morphine. However, subjects who received the IV dose did not have analgesia, whereas volunteers given the drug epidurally did, implying a spinal mechanism of action (16,19). In the case of a hydrophilic drug, uptake by epidural fat is probably not significant in reducing systemic absorption (10).

After epidural injection of lipid-soluble drugs such as meperidine or fentanyl, un-ionized drug diffuses rapidly into epidural veins, segmental arteries, and across both arachnoid granulations and the dural cuff into cerebrospinal fluid. The actual mechanism of analgesia is controversial. Epidural fentanyl most probably acts at both supraspinal (via systemic delivery) and spinal sites, in addition to drug diffusing to spinal receptors from the cerebrospinal fluid (15). Blood concentrations depend in large part on flow dynamics within epidural venous plexus and spinal arteries (10). For example, in situations where inferior vena caval

flow is impaired, such as with aortocaval compression during pregnancy, blood flow from the pelvis and lower extremity can redistribute to the azygous system via the epidural plexus, markedly enhancing flow and drug delivery to the systemic circulation during pregnancy (10).

Interactions with Local Anesthetics

The value of combining local anesthetic and opioids for postoperative pain control has been well established. The combination allows for a reduction in doses of both classes of drugs, thus lessening the likelihood of side effects attributable to each (16). In animals, there may be a synergistic effect on relief of visceral and somatic pain by combining intrathecal morphine and lidocaine (17). After elective cesarean delivery (18), women given epidural fentanyl alone had more pain, more nausea and vomiting, more urinary retention, and less patient satisfaction than when fentanyl was combined with bupivacaine (with or without epinephrine).

Intrathecal Opioids: Analgesic Efficacy and Side Effects

Many opioids, including morphine (19–24), fentanyl (25–28), meperidine (29,30), sufentanil (27), nalbuphine (31), and heroin (32), have been used intrathecally for post-cesarean delivery analgesia.

A single dose of intrathecal morphine at the time of cesarean delivery can provide excellent analgesia of prolonged duration. Morphine, in doses ranging from 0.075 mg (20) to 0.5 mg (24), provides high-quality postoperative analgesia lasting up to 24 h after cesarean delivery. However, there may be a ceiling effect on the dose of intrathecal morphine that results in analgesia. For instance, in one study (20) 108 women undergoing elective cesarean delivery were randomized to receive 1 of 9 doses of intrathecal morphine ranging from 0.025 to 0.5 mg. Twenty-four hour IVPCA morphine use was 45.7 mg less in the 0.075 mg group than in the control group. However, there was no difference in PCA use after doses of intrathecal morphine larger than 0.075 mg. In another study (19), morphine 0.1 or 0.25 mg was administered as a component of spinal anesthesia in 60 women undergoing elective cesarean delivery. Women also received 20 μg of spinal fentanyl and a perioperative and postoperative nonsteroidal antiinflammatory drug (NSAID) routinely. There was no significant difference between the small and larger-dose morphine groups in pain relief as measured by visual analog pain scores. A meta-analysis (33) demonstrated excellent efficacy of morphine doses of 0.1 to 0.2 mg but no additional pain relief with doses >0.2 mg. Median time to first request for supplemental analgesics in that study was 27 h. In contrast, doses smaller than 0.1 mg had little effect on pain relief.

Adverse effects of intrathecal morphine have been reported widely and include pruritus, nausea and vomiting, urinary retention, and early or delayed respiratory depression. Pruritus may be the most frequent and bothersome side effect. Dahl et al. (33) showed that the incidence of pruritus, and nausea and vomiting increased as morphine doses increased from 0.05 mg to 0.25 mg. A randomized prospective study (19) demonstrated a decreased incidence of pruritus and nausea with doses of 0.1 mg as compared with 0.25 mg. In another study, women receiving 0.2 mg versus 0.1 mg of intrathecal morphine for elective cesarean delivery (21) had significantly higher pruritus scores but no difference in postoperative nausea or vomiting. Clinically significant respiratory depression is rare with intrathecal opioids, such as morphine, fentanyl, sufentanil, and buprenorphine (33). Abouleish et al. (34) conducted a prospective study of analgesic efficacy and side effects of 0.2 mg morphine in 856 parturients having spinal anesthesia for elective cesarean delivery. Women were monitored for respiratory depression using pulse oximetry and respiratory rate for 24 h. Respiratory depression was defined as either a Spo_2 <85% or a respiratory rate <10 breaths/min. Eight women (0.93%), all of whom were morbidly obese, had respiratory depression according to these criteria. There is an added concern that pruritus in the trigeminal nerve dermatomes related to neuraxial morphine administration may increase the likelihood of herpes labialis virus type II reactivation (35).

Because of the relatively short duration of analgesia with fentanyl given intrathecally, there may be little long-term benefit to a single dose of fentanyl added to local anesthetic at the time of cesarean delivery. However, Hunt et al. (25) conducted a randomized study that demonstrated a dose-dependent increase in post-cesarean delivery analgesia up to a fentanyl dose of 6.25 μg, beyond which there was no added advantage. Furthermore, mean duration of effective analgesia was only 200 min, and 24-h supplemental opioid use was the same for all groups, including placebo. Initial analgesia (0–6 h postcesarean delivery) may be better with sufentanil (2.5 and 5 μg) than fentanyl (10 μg) (27). Another group (26) randomized 48 women having elective cesarean delivery to intrathecal or IV fentanyl (12.5 μg) at time of bupivacaine spinal. The intrathecal group needed less supplemental analgesics during surgery, and the time to first analgesic request was significantly longer (159 $\pm$ 39 versus 119 $\pm$ 44 min respectively) compared with the IV fentanyl group.

In contrast to morphine, intrathecal use of lipid soluble drugs, such as fentanyl and sufentanil, does not appear to predispose to nausea and vomiting after cesarean delivery but both drugs can cause pruritus (although less severe than morphine) in a dose-related

manner (25–27,36). Paradoxically, either drug, when administered spinally for cesarean delivery with bupivacaine, results in less antiemetic use than when local anesthetic is administered alone (26,27). In a study comparing the effectiveness of IV ondansetron to intrathecal fentanyl for prevention of nausea and vomiting after spinal anesthesia for cesarean delivery, intrathecal fentanyl alone was associated with significantly less risk of nausea (but not vomiting) as compared with a single IV injection of ondansetron (37). The reason for this is unclear but may relate to the increased frequency of hypotension, which itself can cause nausea and vomiting, observed in women having spinal anesthesia in the ondansetron group. The risk of delayed respiratory depression is relatively small with spinal fentanyl and sufentanil, given their segmental effect and lack of rostral spread in the cerebrospinal fluid (10). In one large meta-analysis, there were no cases of respiratory depression with intrathecal fentanyl and sufentanil (33). If respiratory depression does occur, it usually manifests within 30 min when using fentanyl or sufentanil.

Other less-commonly used intrathecal opioids include meperidine, diamorphine (heroin), buprenorphine, and, nalbuphine. Meperidine has been studied extensively, and its analgesia and side effects cannot be distinguished from fentanyl (29,30). A disadvantage of meperidine for post-cesarean delivery pain relief is that, among the opioids, it has a unique local anesthetic-like effect and may result in motor block. Indeed, meperidine has been used as a sole spinal drug for cesarean delivery (38). Intrathecal nalbuphine, which has been compared with morphine for elective cesarean delivery (31), showed some promise because of a less frequent incidence of side effects, but the lack of safety trials in humans limits its use at this time (39). In addition, it is possible that the use of agonist-antagonist opioids may precipitate withdrawal in a substance-abusing parturient.

Epidural Opioids: Analgesic Efficacy and Side Effects

When using an epidural technique for cesarean delivery, opioids can be administered either as a bolus or as a continuous infusion for postoperative pain relief. Some mothers find that the epidural catheter and infusion equipment reduce their mobility, thus limiting the utility of indwelling epidural catheters for postoperative pain, especially for mothers who are bothered by it and wish to be unencumbered when ambulating and caring for and nursing their infants. Nonetheless, continuous epidural infusions of opioids, alone or combined with local anesthetic, result in high-quality analgesia (40,41). Fentanyl is the opioid used most commonly with such infusions. Early studies suggested that the analgesia obtained with an epidural infusion of fentanyl related to systemic absorption and delivery of drug to central receptors (40). More recently, Cohen et al. (41) conducted a randomized, double-blind study of IV versus epidural fentanyl infusion after elective cesarean delivery. Women were randomized to receive either small-dose bupivacaine or saline epidural infusions at 12 mL/h, as well as either epidural or IV fentanyl PCA. Both groups given IV fentanyl required more rapid rates of infusion and larger total doses of fentanyl, reported more pain, had higher plasma fentanyl levels, and had more frequent side effects, including sedation, nausea and vomiting, than their epidural counterparts. No patient experienced respiratory depression or urinary retention during the study period. This study provides additional evidence that epidurally administered fentanyl has a predominant spinal, rather than supraspinal, site of action.

Addition of a small dose of local anesthetic has also been shown to provide superior post-cesarean delivery analgesia over epidural fentanyl alone, having a dose-sparing effect on fentanyl (18). Paech et al. (42) also demonstrated superiority of epidural over IV opioids in a randomized, double-blind cross-over study of patients having elective cesarean delivery. Postoperatively, mothers were connected to both IVPCA and a continuous epidural catheter (used for cesarean delivery) but only one modality was activated at a time (12 h interval) with meperidine in a sequential, double-blind cross-over manner. Patients reported significantly lower pain scores, higher satisfaction, smaller overall meperidine use, smaller plasma concentrations of both meperidine and normeperidine, and less sedation during the epidural as compared with the IV phase of the trial. Of note, 90% of women preferred epidural over IV meperidine. Notwithstanding potential limitations regarding catheter maintenance and impaired mobility, post-cesarean delivery infusion of short-acting opioids, especially with added small-dose local anesthetic, can offer high-quality analgesia while reducing side effects of the same drugs administered IV.

Epidural catheters used for intraoperative anesthesia are often removed at the end of cesarean delivery, because of a perceived risk of infection, concern for spinal hematoma formation (particularly in preeclamptic women), or if the mother is inconvenienced by the catheter. Although parenteral opioids may be used for pain relief after regression of the sensory block, an opportunity exists, in many cases, to administer long-acting opioids into the epidural space before removal of the catheter. Preservative-free morphine is most often used for prolonged post-cesarean delivery analgesia. One randomized dose-response study (43) allowed patients free access to IVPCA after epidural administration of saline or 1 of 4 doses of morphine (1.25, 2.5, 3.75, or 5 mg). Quality of analgesia improved

as the dose of epidural morphine increased to 3.75 mg. Beyond that, there was no difference in analgesic effect as measured by IVPCA use. All women given epidural morphine experienced pruritus, but there was no correlation with the dose of epidural morphine. Analgesia lasted for 18–26 h.

Neuraxial opioids are a popular mode for post-cesarean delivery analgesia for a number of reasons. Because most women undergoing cesarean delivery will do so with an epidural, a spinal, or both, it is easy enough to add a small dose of opioid to the local anesthetic. The commonly used opioids, particularly morphine and fentanyl, have a long history of safe and effective use that has, in the last decade, been validated with randomized, prospective studies. Finally, adverse effects of neuraxial opioids are well-described and although not infrequent, can be classified primarily as "nuisance" side effects that are easily treated, rather than those that are dangerous and life-threatening.

NSAIDs

Pain after cesarean delivery may have at least two components: postoperative (somatic) pain from the wound itself and visceral pain arising from the uterus. Although somatic pain may be relieved by opioids, visceral pain may be more difficult to treat. NSAIDs are effective for relieving pain related to menstrual cramping and, as a result, there has been interest in the use of NSAIDs to treat a component of pain after cesarean delivery. Unfortunately, NSAIDs alone are insufficient to effectively treat post-cesarean delivery pain (44). However, inclusion of NSAIDs in a multimodal approach to pain relief after cesarean delivery has been very successful both in improving the quality of analgesia resulting from systemic or neuraxially administered opioids and reducing side effects (45–48). For instance, use of IM diclofenac 75 mg results in a morphine-sparing effect and a decrease in side effects related to morphine use (45,46). These benefits also apply to women having regional or general anesthesia and to women having intraspinal opioids for pain relief (49–51).

The disadvantages to using NSAIDs relate to the potential for gastrointestinal side effects and platelet dysfunction. In this regard, use of cyclooxygenase (COX-2) inhibitors may be better because they do not inhibit platelet function. However, COX-2 inhibitors are secreted in the breast milk and there is little experience using these drugs in breast-feeding women. NSAIDs such as ibuprofen and the COX-2 inhibitor, rofecoxib, may be used antepartum as tocolytic drugs (52). Thus, there has also been an added concern of using NSAIDs in postpartum women. For instance, there are rare case reports of uterine atony after the use of ketorolac and diclofenac in postpartum women (53,54). However, no firm causal relationship has been established.

There have also been concerns over fetal exposure to NSAIDs. However, these apply predominantly to prenatal administration where the potential for early closure of the ductus arteriosus may lead to pulmonary hypertension. NSAIDs such as ketorolac and ibuprofen are secreted into breast milk, although at small concentrations, and are generally regarded as safe by the American Academy of Pediatricians for use in breast-feeding women (55). However, ketorolac has a "black box" warning by the Food and Drug Administration, and its manufacturer (Roche, Nutley, NJ) stated that the use of ketorolac is contraindicated a) during labor and delivery because it may adversely affect fetal circulation and inhibit uterine contractions and b) in nursing mothers because of the potential adverse effect of prostaglandin inhibitor drugs on the neonate.

New Drugs, New Delivery Systems

Clonidine. Clonidine exerts its antinociceptive effect by stimulating the α_2 adrenergic receptor and modulating pain pathways in the dorsal horn (56). It is effective for both somatic and visceral pain. The addition of clonidine (up to 150 μg) alone to spinal local anesthetic for post-cesarean delivery analgesia has been disappointing (57). Furthermore, the technique results in an unacceptable degree of hypotension, bradycardia, and nausea and vomiting (57). However, a recent study indicated that clonidine could be a useful adjuvant to spinally administered morphine for postoperative pain relief (58). For instance, adding 60 μg of clonidine to 100 μg of morphine in bupivacaine spinal anesthesia prolonged duration of postoperative analgesia and reduced the need for supplemental analgesics, but also resulted in mild intraoperative (but not postoperative) sedation (58). In another study, adding clonidine, 75 or 150 μg, to epidural morphine, 2 mg, prolonged the duration of analgesia after cesarean delivery from a mean $\pm$ SD of 6.27 $\pm$ 1.6 h with morphine alone to 13.25 $\pm$ 3.8 h and 21.55 $\pm$ 6.3 h, respectively, with the combination, without incurring additional side effects (59). A black box warning exists proscribing the use of clonidine (or other angiotensin converting enzyme inhibitors) during the second and third trimester because of the potential for fetal injury and death.

Dexmedetomidine. Dexmedetomidine is the other α_2 adrenergic receptor agonist that has recently been approved for IV use. Like clonidine, it can cause somnolence, which is undesired in postpartum women, but, in general, respiratory variables, such as oxygen saturation and respiratory rate, are better maintained

with dexmedetomidine than with parenterally administered opioids. Unfortunately, there is little experience with routine use of the drug in postpartum women. At this time, dexmedetomidine is not approved for neuraxial use.

Neostigmine. Neuraxial neostigmine produces analgesia by inhibiting degradation of acetylcholine in the spinal cord. Results of studies using neostigmine for postpartum pain relief have been disappointing because of side effects such as nausea, shivering, and sedation (60,61).

Lipid-Encapsulated Morphine. Advances in technology have allowed for a sustained morphine delivery system to be used with epidural analgesia. DepoFoam™ is a lipid-based vehicle consisting of aqueous chambers that package (encapsulate) the active drug, such as morphine (DepoDur™), resulting in sustained release and prolonged analgesia when the drug is administered epidurally. In one study, 5 mg of unencapsulated morphine was compared with encapsulated morphine at doses of 5, 10, and 15 mg administered epidurally at time of cord clamp (62). The 10-mg and 15-mg doses of encapsulated morphine resulted in superior analgesia of longer duration than the unencapsulated drug. There are two concerns that may limit use of the drug in obstetrics. First, the DepoFoam™ vehicle may be lysed in the presence of local anesthetic, releasing a relatively large amount of morphine in the epidural space and risking respiratory depression; because of this concern, the label for DepoDur™ is used. Second, in this small study, there was one case of delayed respiratory depression that responded quickly to naloxone administration in the encapsulated as compared with none in the unencapsulated group (62). Further studies are needed to determine the optimum dose and safety of lipid-encapsulated morphine in obstetric patients. Nonetheless, encapsulated morphine, administered as a single epidural injection, may be a useful single drug regimen for providing prolonged (up to 48 h) post-cesarean delivery analgesia.

Summary

Women undergoing cesarean delivery should have access to high-quality pain relief that is safe and effective. Post-cesarean delivery analgesia can be provided by a variety of means. The choice of technique is frequently influenced by factors such as the use of regional anesthesia or patient preference. Despite ample evidence that neuraxial opioids are superior to parenterally administered opioids in this population, their routine use is often limited by availability of floor personnel needed for appropriate monitoring of side effects, such as delayed respiratory depression. Finally, adjuvants, such as NSAIDs, α_2-agonists, and anticholinergics, may play a significant role in enhancing the analgesic efficacy of traditional parenteral or neuraxial opioid-based techniques after cesarean delivery while at the same time decreasing the potential for side effects by reducing opioid requirements.

References

1. Austin KL, Stapleton JV, Mather LE Multiple intramuscular injections: a major source of variability in analgesic response to meperidine. Pain 1980;8:47–62.
2. Austin KL, Stapleton JV, Mather LE. Relationship between blood meperidine concentration and analgesic response. Anesthesiology 1980;53:460–6.
3. Sechzu PH. Objective measurement of pain. Anesthesiology 1968;29:209–10.
4. Eisenach JC, Grice SC, Dewan DM. Patient-controlled analgesia following cesarean section: a comparison with epidural and intramuscular narcotics. Anesthesiology 1988;68:444–8.
5. Wittels B, Scott DT, Sinatra RS. Exogenous opioids in human breast milk and acute neonatal behaviour: a preliminary study. Anesthesiology 1990;73:864–9.
6. Parker RK, Holtman B, White PF. Patient-controlled analgesia: does a concurrent opioid infusion improve pain management after surgery. JAMA 1991;266:1947–52.
7. Wang JK, Nauss LE, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology 1979;50:149–51.
8. Hawkins JL, Gibbs C, Orleans M, et al. Obstetric anesthesia workforce survey. Anesthesiology 1997;87:135–43.
9. Jenkins JG, Khan MM. Anaesthesia for Caesarean section: a survey in a UK region from 1992 to 2002. Anaesthesia 2003;58: 1114–8.
10. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.
11. Bromage PR, Camporesi EM, Durant PAC, Nielsen CH. Rostral spread of epidural morphine. Anesthesiology 1982;46:431–6.
12. Yaksh TL, Noueihed RY, Durant AC. Studies of the pharmacology and pathology of intrathecally administered 4-aminopiperidine analogues and morphine in the rat and cat. Anesthesiology 1986; 64:54–66.
13. Nordberg G, Hedner T, Mellstrand T, Dahlstrom B. Pharmacokinetic aspects of epidural morphine analgesia. Anesthesiology 1983;58:545–51.
14. Wedel SJ, Ritter RR. Serum levels following epidural administration of morphine and correlation with relief of post surgical pain. Anesthesiology 1981;54:210–4.
15. Mather LE, Cousins MJ. The site of action of epidural fentanyl: what can be learned by studying the difference between infusion and bolus administration? The importance of history, one hopes. Anesth Analg 2003;97:1211–3.
16. de Leon-Casasola OA. Clinical outcome after epidural anesthesia and analgesia in high-risk surgical patients. Reg Anesth 1996;21:144–8.
17. Maves TJ, Gebhart GF. Antinociceptive synergy between intrathecal morphine and lidocaine during visceral and somatic nociception in the rat. Anesthesiology 1992;76:91–9.
18. Cohen S, Lowenwirt I, Pantuck CB, et al. Bupivacaine 0.01% and/or epinephrine 0.5 mcg/ml improve epidural fentanyl analgesia after cesarean section. Anesthesiology 1998;89:1354–61.
19. Yang T, Breen TW, Archer D, Fick G. Comparison of 0.25 mg and 0.1 mg intrathecal morphine for analgesia after Cesarean section. Can J Anaesth 1999;46:856–60.
20. Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose-response relationship of intrathecal morphine for postcesarean analgesia. Anesthesiology 1999;90:437–44.
21. Sarvela J, Halonen P, Soikkeli A, Korttila K. A double-blinded, randomized comparison of intrathecal and epidural morphine for elective cesarean delivery. Anesth Analg 2002;95:436–40.
22. Abouleish E, Rawal N, Tobon-Randall B, et al. A clinical and laboratory study to compare the addition of 0.2 mg of morphine, 0.2 mg of epinephrine, or their combination to hyperbaric bupivacaine for spinal anesthesia in cesarean section. Anesth Analg 1993;77:457–62.

23. Swart M, Sewell J, Thomas D. Intrathecal morphine for caesarean section: an assessment of pain relief, satisfaction and side-effects. Anaesthesia 1997;52:373–7.
24. Chadwick HS, Ready LB. Intrathecal and epidural morphine sulfate for postcesarean analgesia: a clinical comparison. Anesthesiology 1988;68:925–9.
25. Hunt CO, Naulty JS, Bader AM, et al. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. Anesthesiology 1989;71:535–40.
26. Siddick-Sayyid SM, Aouad MT, Jalbout MI, et al. Intrathecal versus intravenous fentanyl for supplementation of subarachnoid block during cesarean delivery. Anesth Analg 2002;95:209–13.
27. Dahlgren G, Hultstrand C, Jakobsson J, et al. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesth Analg 1997;85:1288–93.
28. Sibilla C, Albertazzi P, Zatelli R, Martinello R. Perioperative analgesia for caesarean section: comparison of intrathecal morphine and fentanyl alone or in combination. Int J Obstet Anesth 1997;6:43–8.
29. Roy J, Girard M, Drolet P. Intrathecal meperidine decreases shivering during cesarean delivery under spinal anesthesia. Anesth Analg 2004;98:230–4.
30. Yu S, Ngan Kee WD, Kwan ASK. Addition of meperidine to bupivacaine for spinal anaesthesia for Caesarean section. Br J Anaesth 2002;88:379–83.
31. Culebras X, Gaggero G, Zatloukal J, et al. Advantages of intrathecal nalbuphine, compared with intrathecal morphine, after cesarean delivery: an evaluation of postoperative analgesia and adverse effects. Anesth Analg 2000;91:601–5.
32. Kelly MC, Carabine UA, Mirakhur RK. Intrathecal diamorphine for analgesia after Caesarean. Anaesthesia 1998;53:231–7.
33. Dahl JB, Jeppesen IS, Jorgensen H, et al. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia. Anesthesiology 1999;91:1919–27.
34. Abouleish E, Rawal N, Rashad MN. The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. Reg Anesth 1991;16:137–40.
35. Crone LA, Conley JM, Storgard C, et al. Herpes labialis in parturients receiving epidural morphine following cesarean section. Anesthesiology 1990;43:208–13.
36. Belzarena SD. Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section. Anesth Analg 1992;74:653–7.
37. Manullang TR, Viscomi CM, Pace NL. Intrathecal fentanyl is superior to intravenous ondansetron for the prevention of perioperative nausea during cesarean delivery with spinal anesthesia. Anesth Analg 2000;90:1162–6.
38. Kafle SK. Intrathecal meperidine for elective Cesarean section: a comparison with lidocaine. Can J Anaesth 1993;40:718–21.
39. Yaksh T, Birnbach DJ. Intrathecal nalbuphine after Cesarean delivery: are we ready? Anesth Analg 2000;91:505–8.
40. Ellis DJ, Millar WL, Reisner LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after Cesarean section. Anesthesiology 1990;72:981–6.
41. Cohen S, Pantuck CB, Amar D, et al. The primary action of epidural fentanyl after Cesarean delivery is via a spinal mechanism. Anesth Analg 2002;94:674–9.
42. Paech MJ, Moore JS, Evans SF. Meperidine for patient-controlled analgesia after cesarean section. Anesthesiology 1994;80:1268–76.
43. Palmer CM, Nogami WM, Van Maren G, Alves DM. Postcesarean epidural morphine: a dose-response study. Anesth Analg 2000;90:887–91.
44. Lowder JL, Shackelford D, Holbert D, Beste T. A randomized, controlled trial to compare ketorolac tromethamine versus placebo after cesarean section to reduce pain and narcotic usage. Am J Obstet Gynecol 2003;189:1559–62.
45. Cardoso M, Carvalho J, Amaro A, et al. Small doses of intrathecal morphine combined with systemic diclofenac for postoperative pain control after cesarean delivery. Anesth Analg 1998;86:82–6.
46. Hodsman NBA, Burns J, Blyth A, et al. The morphine sparing effects of diclofenac sodium following abdominal surgery. Anaesthesia 1987;42:1005–8.
47. Gilles G, Kenny G, Bullingham R, McCardle C. The morphine sparing effect of ketorolac tromethamine: a study of a new, parenteral nonsteroidal anti-inflammatory agent after abdominal surgery. Anaesthesia 1987;42:727–31.
48. O'Hara D, Franciullo G, Hubbard L, et al. Evaluation of the safety and efficacy of ketorolac versus morphine by patient-controlled analgesia for postoperative pain. Pharmacotherapy 1997;17:891–9.
49. Dennis A, Leeson-Payne C, Hobbs G. Analgesia after cesarean section. Anaesthesia 1995;50:297–9.
50. Luthman J, Kay NH, White JB. The morphine sparing effect of diclofenac sodium following caesarean section under spinal anaesthesia. Int J Obstet Anesth 1994;3:82–6.
51. Bush D, Lyons G, Macdonald R. Diclofenac for analgesic after caesarean section. Anaesthesia 1992;47:1075–7.
52. McWhorter J, Carlan SJ, O'Leary JD et al. Rofecoxib versus magnesium sulfate to arrest preterm labor: randomized trial. Obstet Gynecol 2004;103:923–30.
53. Diemunsch P, Alt M, Diemunsch A, Treisser A. Post cesarean analgesia with ketorolac tromethamine and uterine atonia. Eur J Obstet Gynecol Repro Biol 1997;72:205–6.
54. Roarius MG, Suominen P, Baer G, et al. Diclofenac and ketoprofen for pain treatment after elective caesarean section. Br J Anaesth 1993;70:293–7.
55. The American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776–85.
56. Eisenach JC, De Kock M, Klimscha W. Alpha$_2$-adrenergic agonists for regional anesthesia: a clinical review of clonidine (1984–1995). Anesthesiology 1996;85:655–74.
57. Pan PM, Huang CT, Wei TT, Mok MS. Enhancement of analgesic effect of intrathecal neostigmine and clonidine in bupivacaine spinal anesthesia. Reg Anesth Pain Med 1998;23:49–53.
58. Paech MJ, Pavy TJG, Orlikowski CE, et al. Postcesarean analgesia with spinal morphine, clonidine or their combination. Anesth Analg 2004;98:1460–6.
59. Capogna G, Celleno D, Zangrillo A, et al. Addition of clonidine to epidural morphine enhances postoperative analgesia after cesarean delivery. Reg Anesth 1995;20:57–61.
60. Krukowski JA, Hood DD, Eisenach JC, et al. Intrathecal neostigmine for post-cesarean section analgesia: dose response. Anesth Analg 1997;84:1269–75.
61. Eisenach JC, Owen MD, Kaya N, Sahin S Epidural neostigmine for postcesarean section analgesia [abstract]. Anesthesiology 2003;98(Suppl 1):A40.
62. Carvalho B, Cohen SE, Gambling RD, et al. Epidural sustained-release encapsulated morphine (SKY 0401) in the management of postoperative pain following cesarean section [abstract]. Anesthesiology 2003;98(Suppl 1):A3.