Abstract: Cesarean section patients have compelling reasons to achieve optimal postoperative pain relief, because they are expected to recover expeditiously and to care for their newborns within a few hours following surgery. Consequently, it is necessary that pain relief is safe and effective, that it does not interfere with the mother’s ability to care for her infant, and that it results in no adverse neonatal effects in breast-feeding women. However, although research in this field is increasing, there is no ‘gold standard’ for post-caesarean pain management. Most methods rely on opioids, supplemented with non-opioid analgesics, nerve blocks or other adjunctive techniques. The aim of this manuscript is to evaluate and compare through literature review commonly used opioid- and non-opioid-based methods, when incorporated into a multimodal approach to post-caesarean pain management. Areas of promising research are also discussed.

Key words: Cesarean section; cesarean delivery; obstetrical anesthesia; postoperative pain; post-caesarean analgesia; opioid analgesia; spinal analgesia; intrathecal opioids; epidural opioids; patient-controlled analgesia; systemic opioids; nerve blocks; wound infiltration; transversus abdominis plane block.

Introduction

Cesarean section is one of the most commonly performed surgical procedures. It is estimated that about 15% of births worldwide and 21.1% of those in western countries occur through a cesarean section (1). Over one million cesarean deliveries are thought to be carried out annually in the USA alone (2). The general advantages derived from relieving postoperative pain in surgical patients have been summarized elsewhere and apply also to women undergoing cesarean delivery. However, cesarean section patients have even more compelling reasons to benefit from optimal postoperative pain relief. Cesarean sections differ from other major laparotomies because women are expected to recover expeditiously and to care for their newborns within a few hours following surgery. Therefore, women after cesarean delivery are reluctant to feel drowsy, sleepy or restricted by equipment that does not allow them freely attending to their babies. Furthermore, an ideal post-caesarean analgesic regimen must be cost-effective, simple to implement and with minimal impact on staff workload. Drug transfer into breast milk must also be minimal, with no adverse effects on the newborn. However, several other factors, including patient and anesthesiologist preferences, maternal medical situations such as pre-eclampsia or bleeding disorders, staff education and drug availability can influence the choice of the analgesic regimen. When questioning parturient women’s fears and expectations, pain during and after cesarean section is the greatest concern. This concern is immediately followed by vomiting, nausea, cramping, pruritus and shivering (3).

Post-cesarean pain consists of a somatic and visceral component (4). Visceral pain originates from uterine incision and contractions. The somatic component arises from nociceptors within the surgical wound. Nerves supplying the anterior abdominal wall are derived from T6 to L1 and pass through the plane between the layers of the transversus abdominis and internal oblique muscles (4).

The inherent inter-individual variability in the severity of postoperative pain is influenced by multiple factors, such as individual sensitivity to pain, psychological factors (e.g., state of anxiety and somatization), age and genetic factors (5, 6). Ideally, the intensity of post-caesarean pain should be predicted as to customize analgesia. Although the design of multifactorial predictive models for postoperative pain and analgesic requirement is still in its infancy, recent research has evidenced some important predictors, including maternal expectations, anxiety and thermal and electrical pain threshold in the lower back near the dermatomes of the surgical wound (5, 6, 7).
Chronic pain, which is defined as pain that persists beyond the usual course of an acute disease or after a reasonable time for healing (this period can vary from 2 to 6 months), is being recognized as a complication of cesarean delivery. One small survey found that, 6 months after cesarean delivery, 12.3% of patients experience pain that is severe enough to affect infant care (8). In the same study, the incidence of persistent daily pain one year after cesarean section was 6%. Consequently, with millions of cesarean sections annually worldwide, even a small prevalence of persistent pain carries important social and economic consequences.

Poorly controlled pain in the early post-operative period may contribute to the generation of chronic pain (9, 10). Other strong predictors for persistent post-cesarean pain are previous chronic pain states and general anesthesia (8).

Chronic pain and postnatal depression (affecting 8-15% of postpartum women) commonly co-exist (11). In a multicenter, prospective, longitudinal cohort study in which 1288 women hospitalized for cesarean or vaginal delivery were enrolled, Eisenach et al. found a 2.5-fold increased risk of chronic pain and a 3-fold increased risk of postpartum depression among mothers with severe acute postpartum pain, independent of the type of delivery (10).

In this review, we summarize the various drugs and techniques available for relieving acute pain after cesarean delivery (see also Table 1).

**Multimodal analgesic therapy**

Opioids are still playing a central role in post-cesarean pain management (12). From all published data, however, it is clear that opioids alone do not completely relieve pain after cesarean section (12). This finding emphasizes the importance of multimodal or balanced analgesia, that is combining analgesics of different classes or with different mechanisms of action. The aim of this approach is to improve analgesia and to decrease the amount of opioids that is needed to achieve pain relief, thus decreasing the incidence of opioid-related side effects (13).

**Neuraxial analgesia**

Both regional and general anesthesia are used for cesarean delivery, with different advantages and disadvantages (14). During the last decades however, regional anesthesia has been increasingly used for both elective and emergency cesarean section (15). Controversy exists in the current literature regarding the preferable type of anesthesia. In one meta-analysis, the authors concluded that there was no evidence that regional anesthesia was superior to general anesthesia in terms of major maternal or neonatal complications. However, in that meta-analysis, the primary outcome of maternal and neonatal death was omitted. Moreover, decreased blood loss was found in the regional technique group (16). Nevertheless, in another study, anesthesia-related maternal deaths that occurred between 1991 and 2002 in the United States were reviewed. Although case-fatality rates for general anesthesia are currently falling, the mortality risk ratio between general and regional anesthesia is still 1.7 (17).

Neuraxial opioids differ primarily in their potency, onset, duration of action and side effects (18, 19). The value of local anesthetic and opioid co-administration for post-cesarean pain control has been well documented. This combination allows reducing doses of both classes of drugs, thus lessening the likelihood of adverse effects attributable to each (20, 21).

**Intrathecal opioids**

Spinal anesthesia is commonly used for cesarean section, and it has become a popular practice to add opioids to the local anesthetic solution to enhance and prolong the intraoperative and postoperative analgesia. When administered in the subarachnoid space, they appear to act principally on µ-receptors in the substantia gelatinosa of the dorsal horn, by suppressing excitatory neuropeptide release from the C fibers. Following intrathecal injection, onset and duration of action are profoundly affected by the opioid’s pharmacokinetic behavior, and in particular, lipid solubility. Lipid-soluble compounds enjoy greater direct diffusion from the cerebrospinal fluid into the neural tissue. Fentanyl and sufentanil are, respectively, approximately 800 and 1600 times more soluble in lipids than morphine. Consequently, when administered neuraxially, they will exhibit a faster onset, but also a shorter duration of action as compared with morphine (22, 23). Affinity for the µ-receptor is also important for determining the duration of analgesia. For instance, sufentanil, which is considerably more soluble in lipids than fentanyl, and therefore expected to be shorter-acting, has a longer duration of action (24).

Vascular reabsorption of opioids following intrathecal administration does occur to some degree,
Table 1

Summary table

Note: A multimodal approach is recommended whenever possible to maximize pain relief while minimizing untoward effects.

<table>
<thead>
<tr>
<th>Route</th>
<th>Drug</th>
<th>Pro’s</th>
<th>Con’s</th>
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<tbody>
<tr>
<td>NEURAXIAL</td>
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<td>INTRATHECAL</td>
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<tr>
<td></td>
<td>Morphine</td>
<td>Gold standard</td>
<td>Dose-dependent pruritus</td>
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<td></td>
<td></td>
<td>Cost-effective</td>
<td>Dose-independent PONV</td>
</tr>
<tr>
<td></td>
<td>Diamorphine</td>
<td>Quicker onset and increased duration of action compared to IT morphine</td>
<td>Pruritus and vomiting at higher doses</td>
</tr>
<tr>
<td></td>
<td>Fentanyl/Sufentanil</td>
<td>Excellent intraoperative analgesia</td>
<td>Little postoperative analgesic benefit</td>
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<tr>
<td></td>
<td>Meperidine = Pethidine</td>
<td>Can be used in patients with contraindication to local anesthetics</td>
<td>Underdrate motor blockade due to local anesthetic properties</td>
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<td></td>
<td>Naltropine</td>
<td>More favorable side effect profile compared to IT morphine</td>
<td>PONV</td>
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<td></td>
<td>Clonidine (adjunct)</td>
<td>Prolonged postoperative analgesia</td>
<td>Less pain control</td>
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<td></td>
<td>Dexmedetomidine (adjunct)</td>
<td>Encouraging results in lower abdominal surgery</td>
<td>More studies required</td>
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<td></td>
<td>Neostigmine (adjunct)</td>
<td>Reduces postoperative morphine requirements</td>
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<td>Magnesium (adjunct)</td>
<td>Reduces postoperative morphine requirements</td>
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<td>EPIDURAL</td>
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<td></td>
<td>Morphine</td>
<td>Good postoperative analgesia</td>
<td>Less pain compared to IT diamorphine</td>
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<tr>
<td></td>
<td>Diamorphine</td>
<td>Good postoperative analgesia</td>
<td>More favorable side effect profile compared to IT morphine</td>
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<td>Less pain compared to IT diamorphine</td>
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<td>Meperidine = Pethidine</td>
<td>Little postoperative analgesic benefit</td>
<td>More favorable side effect profile compared to IT morphine</td>
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<td>Nalbuphine</td>
<td>Less pain compared to IT diamorphine</td>
<td>More favorable side effect profile compared to IT morphine</td>
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<td>Clonidine (adjunct)</td>
<td>Prolonged postoperative analgesia</td>
<td>More favorable side effect profile compared to IT morphine</td>
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<td>INTRAVENOUS</td>
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<td>Morphine</td>
<td>Appropriate for PCEA</td>
<td>Low risk of drug exposure in breastfed infants</td>
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<td>Fentanyl</td>
<td>Appropriate for PCEA</td>
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<td>INTRAMUSCULAR and SUBCUTANEOUS</td>
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<td>ORAL</td>
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<td></td>
<td>Oxycodone</td>
<td>Low cost-price</td>
<td>High cost-price</td>
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<td></td>
<td>Morphine</td>
<td>Ease of administration</td>
<td>High cost-price</td>
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<td>LOCAL ANESTHETIC TECHNIQUES TARGETING PERIPHERAL NERVE AFFERENTS</td>
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<td>Ilioinguinal and iliohypogastric (IIH) NERVE BLOCK</td>
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<td>WOUND INFILTRATION TAP BLOCK</td>
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<td>SYSTEMIC ADMINISTRATION OF NON-OPIOID ANALGESICS</td>
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<td></td>
<td>Paracetamol</td>
<td>Little risk associated with paracetamol therapy</td>
<td>Potential problems with bleeding, placental dysfunction and renal insufficiency</td>
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<tr>
<td></td>
<td>Nonsteroidal antiinflammatory drugs</td>
<td>Targets also the vascular component of post-cesarean section pain</td>
<td>Potential problems with bleeding, placental dysfunction and renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>COX2 inhibitors</td>
<td>Well-documented opioid sparing effects</td>
<td>Risk of uterine atony in postpartum period</td>
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<td></td>
<td>Ketamine</td>
<td>Decrease NSAID-related adverse effects (on platelet and gastro-intestinal systems)</td>
<td>Poorly studied in literature</td>
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<tr>
<td></td>
<td>Gabapentin</td>
<td>Anti-hyperalgesic properties</td>
<td>Poorly studied in literature</td>
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but is clinically irrelevant in terms of both maternal side effects and effects on the breastfeeding infant, as the doses typically used in the spinal space are small (24). This finding is of great importance, particularly for breast-feeding women and is an advantage of neuraxial modes of post-caesarean analgesia as compared with the larger doses of opioids required systemically.

The use of intrathecal morphine, diamorphine, fentanyl, sufentanil, meperidine, nalbuphine and buprenorphine for post-caesarean pain management is described hereafter.

Intrathecal morphine

Intrathecal morphine, as part of a multimodal analgesic regimen, is a common and effective strategy for providing post-caesarean delivery analgesia and is often seen as the “gold standard” treatment. Indeed, it meets the criteria of ease of administration, good side effect profile, minimal to no effects on fetus through breastfeeding and highly effective at controlling pain (25, 26). Palmer et al. randomized 108 parturient women undergoing cesarean delivery at term to receive a single dose of intrathecal morphine (from 0 to 500 µg) (25). Morphine consumption through a patient-controlled analgesia (PCA) device appeared to be fairly stable in patients receiving a dose between 75 and 500 µg, suggesting a ceiling analgesic effect with doses above 75 µg. Despite a more than fivefold increase in the dose of intrathecal morphine, analgesia remained largely unchanged. However, pruritus severity was found to be directly linked to intrathecal morphine dosage. In contrast, other common opioid-related side effects, such as nausea and vomiting, were not found to have any dose-dependent relationship. In conclusion, the data of this study indicate that there is little justification for the use of more than 0.1 mg of morphine intrathecally for post-caesarean analgesia.

Both intrathecal and epidural morphine share a similar side effect profile. The five classic side effects are pruritus, nausea and vomiting, urinary retention, oral herpes reactivation and respiratory depression (22). A meta-analysis revealed that the number of patients needed to be treated with 50 to 250 µg of intrathecal morphine to harm one individual (NNH) was 2.6 (95% CI, 2.1-3.3) for pruritus, 6.3 (95% CI: 4.2-12.5) for nausea, and 10.1 (95% CI: 5.7-41.0) for vomiting, respectively (19). When administering the dose recommended by Palmer et al. (100 µg) to 100 parturient patients scheduled for cesarean section, 43 women will experience pruritus, 10 will be nauseous and 12 will experience vomiting postoperatively. All of them would not have experienced these side effects without treatment (19).

Morphine delivered via neuraxial (both intrathecal and epidural) routes increases the risk of herpes labialis (oral herpes) reactivation (27). Consequently, a primary concern from this side effect is the risk of maternal transmission to the neonate. However, withholding the benefits of these cost-effective analgesic techniques outweigh the risk of the small possibility of transmitting herpes simplex virus (HSV) to the newborn (27).

Although rare, respiratory depression is a potentially serious risk after neuraxial opioid administration, with an estimated incidence ranging from 0% to 0.9% (28). After intrathecal morphine, respiratory depression is usually delayed, due to rostral spread in cerebrospinal fluid and slow penetration in the brainstem. This risk is not significantly increased with neuraxial compared with parenteral opioid administration (28).

To the best of our knowledge, few data exist about prenatal and postnatal exposure to morphine after a subarachnoid injection. Despite its long history of use, only one case report illustrates the safety of intrathecal morphine in lactating mothers (29).

Intrathecal diamorphine

Diamorphine, which is commonly used in the United Kingdom to provide analgesia after surgery (30), has several desirable properties for use as an analgesic through an intrathecal route. Due to its high lipophilicity, it has a quicker onset of action as compared with morphine. Although diamorphine has a short half-life into the cerebrospinal fluid, it diffuses into neural tissues, and is de-acetylated into its active metabolites 6-mono-acetylmorphine and morphine. Those events increase its duration of action (31). Intrathecal diamorphine has been shown to be as effective as morphine for post-caesarean analgesia (32). Moreover, when administered intrathecally, diamorphine 250 µg has been found to be as effective as fentanyl 15 µg during surgery for cesarean delivery (33). Consequently, diamorphine is an attractive opioid in providing both intra- and prolonged postoperative analgesia. Several studies have indicated that the optimum dose of diamorphine is between 250 and 375 µg, with more side effects at the higher end of the dose range, among which itching and vomiting are particularly frequent (31, 33).

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Intrathecal fentanyl or sufentanil

Intrathecal fentanyl and sufentanil provide excellent intraoperative analgesia (34, 35, 36) and are widely given for this purpose. Because of their relatively short duration of action, however, there is little postoperative analgesic benefit to a single dose added to the local anesthetic solution at the time of cesarean delivery. Moreover, they do not reduce opioid consumption during the first 24 postoperative hours (35). Given its higher $\mu$-receptor affinity, initial analgesia (0-6 h post-cesarean section) may be slightly better with sufentanil (2.5 and 5 $\mu$g) than with fentanyl (10 $\mu$g) (35). The combination of one of these opioids with morphine offers no advantage over intrathecal morphine alone (34, 37).

The incidence of pruritus is very high, but similar, with spinal morphine, fentanyl and sufentanil. However, nausea and vomiting occur less frequently as compared with morphine (19). Finally, the risk of delayed respiratory depression is relatively small with intrathecal fentanyl and sufentanil, due to their segmental effect and lack of rostral spread in the cerebrospinal fluid (28).

Intrathecal meperidine (= pethidine)

Meperidine is an opioid of intermediate lipid solubility and is unique in having significant local anesthetic properties, which can lead to undesirable motor blockade in patients desiring active ambulation during the postoperative period (38). It can be used as the sole spinal drug for cesarean delivery, particularly in those with contraindication to local anesthetic agents (39, 40). In a randomized, double-blind controlled trial, the addition of meperidine 10 mg to intrathecal bupivacaine prolonged post-cesarean analgesia compared with placebo (38). However, the duration of effective analgesia was limited to approximately 4 h, and the overall cumulative morphine consumption at 24 h was similar in both the meperidine group and the control group. Moreover, spinal meperidine 10 mg was found to be associated with more nausea and vomiting than fentanyl and sufentanil (41), which has further limited its popularity.

Intrathecal nalbuphine or buprenorphine

Nalbuphine 0.8 mg (42) and buprenorphine 50 and 150 $\mu$g (43, 44) have been administered neuraxially for post-cesarean analgesia, although more rarely than other opioids. Despite a more favorable side effect profile than intrathecal morphine, women generally experience less pain control with those medications. Consequently, the evidence to support their use in an obstetric setting is currently not strong enough.

Epidural opioids

Epidural infusions of local anesthetic agents alone may be used for postoperative analgesia, but, in general, they are not as effective at controlling pain as local anesthetic-opioid combinations (45). The general mechanism of action of epidural opioids is somewhat the same as after intrathecal injection, with, however, both spinal and supraspinal (via systemica delivery) sites of action (45). This complexity is due to the presence of a dural barrier, to epidural fat that act as a drug depot compartment, and to the increased vascularity of the epidural compartment during pregnancy. The epidural space contains an extensive venous plexus. Therefore, the intravascular reabsorption of opioids following epidural administration is extensive. Epidural administration of morphine, fentanyl, or sufentanil produces opioid blood concentrations that are similar to an intramuscular injection of an equivalent dose (22).

Morphine’s low lipid solubility and prolonged duration of action often allows a single bolus dose offering satisfactory analgesia for the first 24 hours. More lipid-soluble opioids, such as fentanyl and sufentanil have a shorter duration of action, rendering them better suited to patient- or nurse-controlled PCEA techniques in combination with low-dose local anesthetic agents.

A concern regarding epidural analgesia is a possible impact on breastfeeding. An Australian retrospective trial with 1280 women demonstrated an association, but not a causal link, between epidural usage and breastfeeding success (47). However, at this moment, there is no prospective, randomized evidence that epidural analgesia causes reduced breastfeeding success (48). In contrast, in a randomized controlled trial, Wilson et al. found no effect of epidural fentanyl on breastfeeding initiation and duration (49).

Epidural morphine

Palmer et al. conducted a dose-response study with epidurally administered morphine for post-cesarean pain management. Similarly to intrathecal administration, a ceiling effect became apparent (50). Their data indicate that the degree and duration of analgesia increase in a dose-related manner with the dose of epidural morphine from 0 to 3.75 mg. Even the smallest dose in this series,
1.25 mg, had a modest PCA morphine-sparing effect that persisted throughout the 24-hour study period. However, analgesia (as measured by PCA morphine use) was not enhanced when increasing the dose above 3.75 mg up to 5 mg (Fig. 1). Furthermore, parturients continued to use the intravenous morphine PCA at a relatively constant rate, even in the large-dose groups. The latter finding lends further support to the theory of the importance of both spinal and supraspinal opioid receptor occupation.

The general side effect profile of epidural morphine is somewhat the same as with intrathecal morphine. Pruritus and post-operative nausea and vomiting (PONV), however, tend to be less related to dose when administered epidurally (50).

In the last decade, no randomized controlled studies compared the use of intrathecal and epidural morphine for elective cesarean delivery. In 2002, Sarvela et al. randomized 150 parturients scheduled for elective cesarean section into a double-blinded trial to receive intrathecal morphine 0.1 mg (IT 0.1 group) or 0.2 mg (IT 0.2 group) or epidural morphine 3 mg (epidural group) (51). All patients additionally received ketoprofen 300 mg/d. Pain control was equally good in all three groups with an overall high maternal satisfaction. Although mothers in the IT 0.1 group requested rescue analgesics more often than in the other groups, the authors concluded that spinal morphine 0.1 mg is superior for post-cesarean analgesia, because of a decreased incidence of itching (Fig. 2).

Epidural meperidine (= pethidine)

Patient-controlled epidural analgesia with meperidine has been shown to produce high-quality...
pain relief in post-cesarean section patients (55, 56, 57, 58). Various regimens have been validated. Usually, it consists of a loading dose (50 mg given epidurally at the end of the operation), followed by 20 to 25 mg boluses with a lock-out interval ranging from 10 to 20 minutes (55, 56, 59). The addition of a continuous background infusion is of no benefit (60). Administration through the epidural route (meperidine PCEA) significantly lowers pain scores, both at rest and during coughing. It increases maternal satisfaction when compared with a meperidine intravenous PCA (57). Subarachnoid morphine 0.2 mg provides superior pain relief than epidural meperidine during the first 12 h, but is associated with more severe maternal nausea and pruritus. Moreover, spinal morphine and meperidine PCEA provides similar patient satisfaction (58). A recent observational study showed that breastfed infants are at low risk of drug exposure when mothers self-administer epidural meperidine after cesarean section (59).

Epidural fentanyl and sufentanil

In so far as fentanyl and sufentanil are lipid soluble, and therefore have a relatively short duration of action, they are better suited to be administered through a patient-controlled epidural technique. The relative analgesic potency of epidural sufentanil as compared with fentanyl is approximately 5. No major differences between these two opioids are found regarding onset, duration and efficacy of post-cesarean section analgesia, when equipotent analgesic epidural doses are administered postoperatively (61).

Early studies have revealed that epidural fentanyl infusions produce similar levels of post-cesarean section analgesia with an equal side effect profile at 12 and 24 h as compared with the intravenous route (62). When compared with epidural pethidine, no difference exist in terms of pain level outcomes, but epidural fentanyl results in more opioid-related side effects and lower maternal satisfaction (63). The clinical benefit of adding a local anesthetic to fentanyl remains uncertain. Although one study revealed a 57% reduction in fentanyl consumption, overall maternal satisfaction was not modified (64). In contrast, another trial showed that the addition of small amounts of local anesthetic agents (0.01% bupivacaine) or epinephrine not only reduces total fentanyl consumption, but also improves patient satisfaction and adverse effect profile (21).

Similarly, the combination of sufentanil 0.75 µg/ml with ropivacaine 0.2% for PCEA after cesarean delivery, leads to more effective pain relief when compared to ropivacaine 0.2% alone, particularly during the early postoperative period (65). In summary, although the clinical benefit is uncertain, most support the analgesic benefit of adding local anesthetic agents to the solution, but this runs the risk of motor blockade.

Choosing between fentanyl and sufentanil

In a large double-blind trial, including 250 par-turient patients scheduled for an elective cesarean section, the investigators randomized patients into two PCEA groups: group F (n = 125) received fentanyl 2 µg/ml with bupivacaine 0.01% and epinephrine 0.5 µg/ml and group S (n = 125) received sufentanil 0.8 µg/ml with bupivacaine 0.01% and epinephrine 0.5 µg/ml. The initial infusion rate was 16 ml/h with on-demand boluses of 3 ml every 15 min (66). Overall maternal satisfaction, pain-scores and side effects during PCEA were not significantly different between groups. Total number of PCA requests was greater for group F than for group S (106.7 ± 312 vs. 70.8 ± 138, P < 0.05). A couple of hours after discontinuation of the PCA, 1 patient in group F and 42 patients who received sufentanil complained of lightheadedness and dizziness (P < 0.0001). Consequently, the authors concluded that epidural sufentanil offers no benefits over fentanyl administered by the same route.

Extended release epidural morphine

In the setting of cesarean section, the primary limitation of epidural analgesia with a single shot of standard morphine is its short duration of action, which is typically less than 24 h. The use of continuous epidural catheter techniques prolongs analgesia but reduces patient mobility and increases the staff workload. Consequently, a long-acting, slow-release opioid such as extended release epidural morphine (EREM) may theoretically be a better analgesic option after cesarean section. Indeed, pain is often more intense on the second post-cesarean section day, when a single shot neuraxial morphine is no longer effective. EREM (DepoDur®) delivers conventional morphine via a multi-vesicular lipid, sustained-release drug-delivery technology (Depo-Foam®), resulting in prolonged drug delivery (67) (Fig. 3). In a multi-center, randomized, controlled trial, the investigators compared a single epidural injection of either 5 mg of standard morphine and 5, 10 or 15 mg of EREM for post-cesarean section pain control (67). A Single EREM dose of 10 and 15 mg resulted in a significant decrease in total

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supplemental opioid consumption (Fig. 4) and VAS-scores (both at rest and with activity) at 24 and 48 h. It is unclear whether this effect is due to the higher morphine dose or the extended release formulation. This prolonged effect into the period of full patient activity is very attractive. Nevertheless, caution must be applied when EREM is administered to women who have had epidural analgesia using a local anesthetic agent, since epidural lidocaine has been shown to alter the pharmacokinetics and drug effects of EREM (68). More research is required to elucidate the mechanisms and implications of this interaction. A major limitation to a more widespread use of EREM is its high cost, which is difficult to justify when cheaper alternatives are available to provide adequate pain relief after the first 24 h (4).

Patient-controlled (epidural) analgesia [PC(E)A]

Patient-controlled analgesia (PCA) is any method of allowing a person in pain to administer their own pain relief medications. PCA can be delivered through oral, intravenous, subcutaneous, intrathecal and, for this chapter most importantly, epidural (PCEA) routes. When activating the delivery system, hospital staff members place limits on the number of doses of analgesic medication per unit of time that will be administered to the patient. There is also a minimum time interval (lockout interval) that must elapse between two administrations. A continuous background infusion super-imposed on patient-controlled boluses can also be implemented, as discussed later on.

Patient controlled techniques have several advantages, including the lack of waiting time for patients before a caregiver can increase the dosage of medication. As a consequence, the patient spends less time in pain, blood drug concentrations are more stable and patients tend to use less medication than in cases in which medication is given according to a pre-determined schedule. Furthermore, PCA reduces staff workload and enhances women satisfaction, due to increased autonomy and feeling of control (69).

The disadvantages of using PC(E)A in post-cesarean section women include a lack of mobility if local anesthetic agents are used, and the fact that those devices are often quite cumbersome. This can potentially interfere with maternal care of the newborn (4). Other drawbacks are related to financial considerations (70), and the necessity for an available skilled professional to troubleshoot eventual inadequate analgesia, device malfunctions and programming errors (71, 72).

The question of administering a background continuous infusion of opioids in addition to PCEA demand mode or not is controversial. In the post-cesarean section settings, patients may not use the
demand mode for various reasons, such as fear for addiction. This may result in inefficient pain control, unless a basal infusion is used. However, this background infusion may decrease the safety of PCEA. Continuing drug administration even if the patient is pain free or sedated may be dangerous (23). Wong et al. (73) and Vercauteren et al. (74) do not recommend the addition of a background infusion as they did not find any additional benefits over the demand-only mode. Moreover, patients in their background infusion group had a higher total drug consumption, and a higher incidence of adverse effects. In contrast, in their randomized, double-blind study after gastrectomy, Komatsu et al. report lower VAS-scores without more serious side effects in the background infusion group as compared with the demand-only PCEA group (75).

Neuraxial adjuncts

In attempts to improve the quality of intraoperative anesthesia and postoperative analgesia, several non-opioid agents have been employed in conjunction with subarachnoid and epidural opioids and/or local anesthetic agents. In particular, the addition of clonidine, an α2-adrenoreceptor agonist, has been widely studied. The addition of clonidine (up to 150 µg) along with spinal bupivacaine for postcesarean section analgesia does not appear to be sufficient (76). In contrast, the combination of subarachnoid morphine 100 µg and at least 60 µg of clonidine was found to increase the duration of postcesarean section analgesia and reduce the need for supplemental analgesic agents. It also mildly increased intraoperative and postoperative sedation (76). In a randomized controlled trial conducted by Capogna et al., adding clonidine 75 or 150 µg to a modest dose of epidural morphine 2 mg prolonged the duration of postcesarean section analgesia from 6.27 hours (control group) to 13.25 and 21.55 hours, respectively (77). Beyond its analgesic properties, clonidine also possesses postoperative antihyperalgesic qualities (78).

Dexmedetomidine is a new highly selective α2-agonist, which has recently been under evaluation as a neuraxial adjuvant. Up to now, its use in the context of cesarean delivery has not yet been investigated. However, the addition of dexmedetomidine 5 µg intrathecally or 1.5 µg/kg epidurally in the setting of lower abdominal surgery seem to be encouraging (79, 80).

In a study of Krukowski et al., intrathecal neostigmine was associated with reduced postoperative morphine requirements, an effect that lasted approximately 10 hours (81). Over the dose range studied (10–100 µg), intrathecal neostigmine produced reductions in morphine use, independently from the administered dose, but a trend towards a dose-dependent increase in the occurrence of nausea and vomiting. This clinical trial suggested that doses lower than or equal to 10 µg may be adequate as an analgesic adjunct, without increasing the risks of nausea. Nonetheless, aforementioned adverse effects have dissipated further research to use neostigmine by this route. In contrast, the risk of postoperative nausea and vomiting appears to be low and independent from the dose when using epidural neostigmine. Administration of 75 to 300 µg epidurally resulted in a global reduction in pain intensity during the first 24 hours from 5.4 ± 0.2 in the saline group to 3.0-3.5 ± 0.3 in the neostigmine groups. This effect was also independent from the administered dose (82). Although these data are encouraging, more studies in obstetric patients are required to validate utility and promote routine use of epidural neostigmine.

Magnesium has anti-nociceptive properties, due to its non-competitive N-methyl-D-aspartate receptor antagonism. It blocks its ion channel in a voltage-dependent manner (83). Intrathecal administration of magnesium sulfate (MgSO4) significantly potentiates opioid antinociception (84, 85). Magnesium sulfate (MgSO4) alone, however, in addition to spinal local anesthetic agents, does not shorten the onset time of sensory and motor blockade, nor prolongs the duration of spinal anesthesia (86). Similarly, addition of 500 mg of magnesium and 1.5 mg of morphine to 10 mL of epidural 0.1% bupivacaine reduces postoperative pain as compared with the addition of morphine or magnesium alone, or with an additive-free solution (87). Up to now, there is limited information about the safety of neuraxial magnesium in humans. However, Goodman reported that accidental administration of 9 g of magnesium through an epidural catheter did not induce any signs or symptoms of focal neurological toxicity (88). A meta-analysis by Lysakowski et al. showed that supplemental magnesium can provide perioperative analgesia without side effects (89).

Systemic administration of opioids

Systemic opioids are used for post-cesarean section pain management on a regular basis, particularly after general anesthesia (12). Opioids can be
administered by nurses on patient’s request or through a PCA device.

**Intravenous opioids**

Patient-controlled intravenous opioids are popular after cesarean section, because of low fluctuation in plasma opioid concentration and consistently high maternal satisfaction. General advantages and disadvantages are the same as with opioids administered through a PCEA device (see above). When compared with neuraxial opioids, intravenous PCA (IV-PCA) is constantly associated with a lower quality of analgesia (90, 91). In terms of patient satisfaction, literature findings are inconsistent. Some studies (92, 93) demonstrated higher satisfaction scores with IV-PCA than with neuraxial opioids. This is probably due to the increased autonomy that comes with a IV-PCA technique. The higher incidence of pruritus with epidural opioids as compared with IV-PCA (Fig. 5) may also have resulted in less maternal satisfaction with the former. In contrast, Egan et al. and Rapp-Zingraff et al. found better satisfaction with epidural morphine, as compared with IV-PCA morphine (91, 94).

Morphine and fentanyl are both appropriate opioids for use through an IV-PCA in obstetrics (4), in contrast to meperidine. Wittels et al. revealed that among nursing parturients after cesarean section, IV-PCA meperidine (= pethidine) was associated with more neonatal neurobehavioral depression than IV-PCA morphine. In this study, nursing infants exposed to morphine remained more alert and oriented to animate human auditory cues than those exposed to meperidine (95). Compared to morphine, alfentanil has a much faster onset of action because of its higher lipid solubility and high un-ionised fraction (89%) in the plasma at physiological pH (96). Consequently, the combination of those two may be advantageous in relation to the speed of onset (97). Although the addition of alfentanil to morphine was found to be beneficial, it adds also significantly to the cost per patient (97). The addition of remifentanil to long-acting intravenous patient-controlled opioids has been investigated after major abdominal surgery, but not yet after cesarean delivery (98). Adding remifentanil to an IV-PCA tramadol administration resulted in better pain scores, lower analgesic agent consumption, and fewer side effects, when compared with tramadol alone. However, the remifentanil analgesic outcome in the morphine-remifentanil group was not as prominent as in the tramadol-remifentanil group (98). Remifentanil crosses the placenta, but appears to be rapidly metabolized, redistributed, or both, and has not been shown to cause adverse neonatal effects (99).

The question of administering a background continuous infusion of opioids in addition to those delivered on demand through the IV-PCA device is as controversial as during PCEA administration. In a recent double-blind study, 60 ASA 1 or 2 patients scheduled for abdominal hysterectomy were randomly allocated to a group receiving a background continuous morphine infusion of 0.5 mg/h (100) in addition to IV-PCA morphine, or to a group not receiving the additional continuous infusion. The continuous basal infusion was not found to lower pain scores during movement or at rest, but induced higher pain intensity, higher opioid usage and more complications such as nausea, vomiting and dizziness. The most likely explanation for these results is the possible development of acute tolerance to the postoperative continuous infusion of morphine and/or opioid-induced hyperalgesia (100). In contrast, a study of White et al. showed opposite findings (101). According to this trial, adding a 0.01 mg/kg/h background infusion of morphine to an on demand scheme results in 25% reduction of total morphine consumption over the first 48 postoperative hours (Fig. 6). It also favors lower pain scores and greater patient satisfaction on a 10-scale numerical rating scale. Noteworthy, although not specifically documented in cesarean section patients, background IV-PCA infusions of opioids in postsurgical patients increase the risk of respiratory depression (102).
possibly fewer opioid-related adverse effects as compared with the intravenous or neuraxial route, and avoidance of IV-PCA device-associated complications (103, 104, 105, 106). Some physicians have concerns about administering an oral medication immediately after an abdominal surgery. They are concerned about the reduced gastrointestinal motility, decreased absorption of the medication, and increased incidence of nausea and vomiting. However, cesarean section is usually performed under regional anesthesia. This type of surgery involves minimal, if any, manipulation of the bowel. Additionally, studies have demonstrated that the early initiation of solid food is well-tolerated after cesarean delivery (107). To enhance patient satisfaction, oral analgesia should be provided at fixed time intervals with additional “on-demand” dosing, rather than leaving it to patient request (103).

Oxycodone, a semi-synthetic opioid derived from thebaine, has been gaining popularity post-cesarean section analgesia (104, 106). In 2005, DaviS et al. compared IV-PCA morphine with a fixed dose combination of oxycodone and paracetamol (5 mg/325 mg tablets, two tablets 3-4-hourly, maximum 12 tablets during the first 24 h) (104). The regimen included intravenous ketorolac 30 mg and unrelieved pain was treated using intramuscular pethidine. Lower pain scores were found at the 6th and 24th postoperative hour in the oral analgesia group (VAS 3.2 ± 1.8 versus 4.1 ± 2.5, p = 0.04 and 2.9 ± 1.7 versus 4.1 ± 2.1, p = 0.004 respectively). In the same group, nausea and drowsiness were also less common at the 6th hour, but nausea was slightly more frequent at 24th hour. In a randomized controlled trial, McDonnell et al. confirmed that a multimodal regimen consisting of regular oral non-opioids and oxycodone provides satisfactory analgesia after cesarean section, resulting in early postoperative analgesia of a similar quality to a regimen based on intrathecal morphine (Fig. 7) (106). Surprisingly, despite a higher incidence of pruritus, the intrathecal morphine regimen was associated with higher maternal satisfaction scores than in the oxycodone-group. This may have probably been a consequence of factors such as less severe episodic pain and less frequent requirements for rescue analgesic medications. It suggests that post-cesarean mothers consider consistently good pain relief more important than side effects such as pruritus. Notwithstanding, despite the evidence of an accumulation of oxycodone in breast milk for up to 72 hours, Seaton et al. state that the use of oral oxycodone (in doses ≥ 90 mg in a 24 h period) for analgesia after cesarean section poses only minimal

Intramuscular and subcutaneous opioids

The advantages of intramuscularly and subcutaneously administered opioids are their ease of administration, low cost and long history of use in postpartum women. However, there are several serious limitations to their use. First, this mode of administration often requires repeated injections, and this may be uncomfortable for the patient. Second, intramuscular or subcutaneous administration provokes peaks and valleys of the opioid blood concentration. Valleys can affect pain relief, while peaks increase the incidence of adverse effects. Obtained blood levels are also likely to vary considerably between individuals. In addition, after the injection, pain relief is not immediate. The time interval needed for the resorption of the drug from the site of injection, and for the drug to reach opioid receptors is variable. In an era of nursing staff shortages, intramuscular and subcutaneous opioids may be inconvenient for the nursing personnel and the patient. Finally, these methods are rarely used in clinical trials and, consequently, poorly reported in the literature.

Oral opioids

Oral opioids are commonly employed as relay analgesic agents after a primary management using neuraxial or intravenous opioids. The potential benefits of using oral opioids as the primary post-cesarean section analgesic method include the ease of administration, low cost, high maternal acceptance,
pain control in women after caesarean section. The diclofenac/tramadol combination is associated with a higher incidence of nausea (113). The results of a recent investigation on the transfer of tramadol and its O-desmethyl metabolite into transitional breast milk, and the assessment of unwanted effects in the breastfed infants were reassuring (115). Short-term maternal use of tramadol during establishment of lactation is compatible with breastfeeding.

**SYSTEMIC ADMINISTRATION OF NON-OPIOID ANALGESIC AGENTS**

**Paracetamol**

The analgesic properties of paracetamol (= acetaminophen) have been attributed to the inhibition of the cyclo-oxygenase type 3 (COX-3) enzyme within the brain, a reduction in central nervous system prostaglandin E2 production and activation of descending serotonergic pathways (116).

When compared with placebo, paracetamol (or its injectable prodrug propacetamol) significantly reduces morphine consumption after major surgery (117). Several earlier studies and a recent meta-analysis have concluded that a paracetamol-non-steroidal anti-inflammatory drug (NSAID) combination works better than paracetamol alone, and, to a lesser extent, than NSAIDs alone (118). In this systematic review, twenty-one (n = 21) studies enrolling 1909 patients were analyzed. The NSAIDs used were ibuprofen (n = 6), diclofenac (n = 8), ketoprofen (n = 3), ketorolac (n = 1), aspirin (n = 1), tenoxicam (n = 1), and rofecoxib (n = 1). The combination of paracetamol and NSAID was found to be more effective in reducing postoperative pain and/or supplementary analgesia than paracetamol or NSAID alone in 85% and 64% of relevant studies, respectively. Of these 21 studies, two are particularly noticeable, because they were conducted in patients beneficiating from a cesarean section, and because diclofenac was the used NSAID in addition to IV or rectal propacetamol (119), followed by oral paracetamol (120). Both studies found that the combination significantly reduced supplementary analgesic consumption, as compared with paracetamol alone, but did not compare with diclofenac alone. Overall, there is little risk associated with paracetamol therapy (111, 117). Hence, it has been suggested as a “near-routine” medication for use within a multimodal post-caesarean section pain management plan. In a recently published article, Kulo et al. showed that peak and trough paracetamol

**Fig. 7. — Area under the curve for scores of rest pain, movement pain and sedation in the first 24 h. No significant differences between groups. Group O : Oral oxycodone ; group I : intrathecal morphine.**

concentrations in women following cesarean delivery were lower than in non-pregnant patients. This is due to a higher clearance and a larger distribution volume. Consequently, in the future, reducing the interval between consecutive doses (typically every 6 hours, at present) or increasing the regular dose (typically 1 g, at present) may be considered during the postpartum period. It emphasizes the need for integrated pharmacokinetic and pharmacodynamic studies related to peripartum analgesia (121).

**Non-steroidal anti-inflammatory drugs (NSAIDs)**

As mentioned above, pain after a cesarean section may have at least 2 components: somatic pain originating from the surgical wound itself, and visceral pain arising from the uterine incision and involution. Although somatic pain may be relieved by opioids, the treatment of visceral pain may reveal more difficult. As NSAIDs are very effective for relieving pain related to menstrual cramping, interest has grown in the use of NSAIDs to treat the visceral component of post-cesarean section pain. Several different NSAIDs and administration routes have been investigated, including ketorolac (122, 123), intramuscular (124) and rectal (125) diclofenac, oral naproxen (126), dipyrone (105), ibuprofen (103) and others. Overall, the addition of NSAIDs to a post-cesarean section analgesic regimen has been very successful, both at improving the quality of analgesia resulting from neuraxial or systemic opioids, and at reducing opioid-related side effects (117, 124). Despite these well-documented opioid-sparing effects and the compatibility with breastfeeding (111), NSAIDs must be used with caution. They carry the risk of bleeding, platelet dysfunction and renal insufficiency. Concern has also been raised with regard to uterine atony during the postpartum period (127). Cases of severe uterine atony associated with a ketorolac (128) or diclofenac (129) administration have been reported. Consequently, the use of NSAIDs in women at risk of postpartum hemorrhage, or suffering from a pre-eclampsia-induced renal impairment deserves caution.

The introduction of the cyclo-oxygenase 2 (COX2) specific inhibitors has the potential to decrease adverse effects, particularly with regard to the platelet and gastro-intestinal systems. When administered in low doses, they are also very unlikely to cause untoward effects in breastfed infants (130, 131). Studies comparing COX2-inhibitors to NSAIDs, have demonstrated similar analgesic efficacy and opioid-sparing effects after non-obstetric surgery (117). However, data related to the obstetric setting are quite limited. **Fong et al.** (132) found that perioperative celecoxib administration (400 mg) improves post-cesarean section analgesia during the first 24 h. **Wong et al.** (133) studied the efficacy of post-cesarean section parecoxib. They allocated 66 parturient patients to two groups: the first group (n = 33) received an initial postoperative 40 mg intravenous bolus of parecoxib as a loading dose, followed by two boluses of 20 mg subsequently given at intervals of 24 h. The other group received a ketorolac-based regimen (postoperative intravenous loading bolus of 30 mg followed by 90 mg of ketorolac combined with morphine into an IV-PCA device). No significant differences in terms of sedative side effects, mood state, quality of sleep and satisfaction were found between the two groups, but there was a lower total morphine requirement (22% reduction) in the parecoxib group (43.5 ± 19.2 versus 55.5 ± 21.5 in the ketorolac and parecoxib group, respectively, p = 0.02). Regarding adverse effects, there were no statistical differences between groups.

**Ketamine**

Due to the central role played by NMDA receptors in central sensitization, NMDA-antagonists, such as ketamine, may be useful for their analgesic and anti-hyperalgesic properties (134). However, available data regarding the efficacy of ketamine against post-cesarean section pain are conflicting. Compared to placebo, **Suppa et al.** (135) found a significantly reduced morphine consumption 4, 8, 12 and 24 h after cesarean section under subarachnoid anesthesia (total 31%) in the group receiving 0.5 mg/kg intramuscular S-ketamine 10 minutes after birth, followed by a 2 µg/kg/min intravenous continuous infusion for 12 h. Several minor side effects (drowsiness, diplopia, positive dysphoria and nystagmus) were observed in the ketamine group, but they were all short-lived and resolved within a few hours. In contrast to the aforementioned study, **Bilgen et al.** found no difference in morphine consumption or pain scores among groups treated with three different doses of intravenous ketamine (0, 0.25, 0.5, and 1 mg/kg) prior to general anesthesia (136). **Bauchat et al.** didn’t find an additional postoperative analgesic benefit of low-dose ketamine (10 mg) either in patients who received intrathecal morphine and intravenous ketorolac (137). The addition of ketamine intrathecally has also revealed disappointing (138). No detrimental effect on uterine blood flow or fetal hemodynamics has
been demonstrated at clinically relevant doses (139). Ketamine is avidly transferred from the placenta, yet intravenous doses up to 2 mg/kg do not lead to reduced Apgar scores in the neonate (136). To our knowledge, no data on its transfer in human breast milk have been published so far.

**Gabapentin**

The perioperative use of gabapentin has been shown to decrease postoperative pain after various surgical procedures (140), including total hysterectomy (141). Recently, Moore et al. investigated its use for the management of post-caesarean delivery pain (142). The results of their randomized controlled trial suggest that, even in the setting of a multimodal regimen that includes intrathecal morphine, intrathecal fentanyl, oral paracetamol, oral diclofenac and systemic opioids for breakthrough pain, a single 600 mg oral dose of gabapentin given 1 hour before cesarean section significantly lowers pain scores during the first 48 postpartum hours and increases maternal satisfaction. Gabapentin is thought to exert its analgesic effect by binding to presynaptic voltage gated calcium channels in the dorsal root ganglia of the spinal cord, where it inhibits the release of excitatory neurotransmitters (140). Gabapentin has also been shown to enhance the analgesic effect of morphine in humans (143). Despite readily crossing through the placenta and transfer to the fetus, no increased risks for adverse fetal or neonatal outcomes (such as low birth weight or malformations) have been attributed to the use of gabapentin during pregnancy (144). The results of the study of Moore et al. are very encouraging, but further research is required to provide information on the optimal dose and timing of gabapentin administration during the peri-operative period of a cesarean section.

**Local anesthetic techniques targeting peripheral nerve afferents**

A significant component of pain after cesarean delivery arises from the surgical incision through the anterior abdominal wall. Multiple local anesthetic techniques targeting peripheral nerve afferents, including ilioinguinal and iliohypogastric (IIII) nerve blocks, wound instillation and, most recently, transversus abdominis plane (TAP) blocks, have been used to address this somatic component of post-caesarean section pain (145). The potential advantages of these techniques are their lower invasiveness as compared with neuraxial blocks, their suitability for patients undergoing general anesthesia (146), and the possibility of repeating them postoperatively if required. Ultrasonography has been used to improve quality and safety of peripheral nerve blockade (147, 148). Instead of relying on fascia “clicks” and “pops”, ultrasound offers real-time guidance and precision in needle placement.

**Ilioinguinal and iliohypogastric (IIII) nerve blocks**

The Pfannensteil incision lies within the L1 dermatome, which is supplied by the iliohypogastric and ilioinguinal nerves. Wolfson et al. found that bilateral IIII nerve blocks using a standardized multi-level injection technique, previously developed by Bell et al. (149), result in lower resting VAS pain scores, lower analgesic requirements and greater satisfaction following caesarean delivery in patients who received neuraxial morphine (145). Despite evidence of efficacy, IIII nerve blocks have a relatively short duration of action. This constitutes a major limitation to their widespread use. A continuous technique has been described, with excellent results, in a small case series (150), but these encouraging data require further investigation.

**Wound infiltration**

Local anesthetic drugs are increasingly administered through the wound following different types of surgery, including gynecological and obstetric procedures, with variable results. This is probably due to differences among studies in catheter placement sites, doses of medications, continuous or intermittent bolus mode of administration, and definition of outcomes. The administration of local anesthetic agents under the fascia has been shown to be more effective than the administration above it (151). Ranta et al. compared epidural analgesia with wound catheters placed under the fascia and receiving intermittent boluses (152). They showed that, during the first 4 postoperative hours, the epidural patients achieved significantly better pain relief, and lower consumption of levobupivacaine. After four hours however, there were no significant differences between the sub-fascia and epidural group regarding pain scores, overall opioid consumption, patient satisfaction and side effects. O’Neill et al. tested a ropivacaine continuous wound infusion regimen and found lower postoperative median pain scores at 2-, 6- and 48-hour when compared to the epidural morphine control-group (153). In contrast, Kainu et al. found no
benefit of a sub-fascia ropivacaine continuous wound infusion after cesarean delivery (154).

Local anesthetic injections into the wound work through a direct inhibition of noxious impulses from the site of injury. Another approach to modulate peripheral nociceptive transmission consists in reducing the local expression of mediators that sensitize nociceptors on afferent fibers. Among these, prostaglandins are potent sensitizing agents. Their release is due to an increased cyclo-oxygenase (COX) expression in immune cells and fibroblasts at the site of injury. A continuous diclofenac infusion (300 mg over 48 hours) through a wound infusion catheter appears to be as effective as a local ropivacaine infusion associated to the same dose of systemic diclofenac (300 mg administered as an intermittent intravenous bolus) (155).

Despite the fact that wound infusion catheters provide prolonged drug delivery, the relatively high cost of the disposable devices and the effort required for the preparation and insertion of those catheters may have limited their widespread acceptance.

**Transversus abdominis plane (TAP) block**

The transversus abdominis plane (TAP) block, whose popularity is growing, is a relatively new technique. It targets the neural afferents of the anterior abdominal wall. The TAP block was first described in 2001 by Rafi (156) and was further developed and tested by McDonnell et al. in 2007 (157). The lumbar triangle of Petit is used as an easy palpable landmark for injecting local anesthetic agents into the neurovascular plane of the abdominal wall. That plane is located between the internal oblique and the transversus abdominis muscles. Nerves supplying the anterior abdominal wall are derived from the T6 to L1 roots, and pass through this plane before supplying the muscles of the anterior abdominal wall. The triangle of Petit is posteriorly bounded by the latissimus dorsi muscle, anteriorly by the external oblique, and inferiorly by the iliac crest. The floor of the triangle is made of fascia extensions of both the external and the internal oblique muscles (Fig. 8). In this triangle, a blunt regional anesthesia needle can be inserted perpendicular to the skin, immediately above the iliac crest, and behind the mid-axillary line. The transversus abdominis fascia plane is localized using a two-‘pop’ sensation (or loss of resistance) technique. The first ‘pop’ indicates penetration of the fascia of the external oblique muscle and the second ‘pop’ indicates penetration of the internal oblique muscle, thereby indicating a position of the needle tip within the transversus abdominis fascia plane. After careful aspiration to exclude vascular puncture, a local anesthetic solution can be injected there. It will block the sensory nerves of the anterior abdominal wall before they leave this plane to innervate the entire anterior abdominal wall (157). This ‘blind’ TAP block technique is easy to perform, and safe (156, 158). However, the triangle of Petit may be difficult to palpate in obese patients (156). TAP blocks also carry the risk of an unintentional peritoneal puncture (159). To reduce risks, the use of ultrasounds is a promising approach (148). In addition, ultrasound guidance reduces the time and number of attempts needed to perform the block, as well as the onset time (148).

In 50 women undergoing elective cesarean delivery, McDonnell et al. compared a ropivacaine 0.75% (1.5 mg/kg to a maximum of 150 mg per side) TAP block and a saline placebo one. Standard postoperative analgesia including IV-PCA morphine, diclofenac and paracetamol was otherwise provided to all patients (158). The TAP blocks with local anesthetic agents reduced overall postoperative morphine requirements by more than 70% during the first 48 postoperative hours (Fig. 9). This finding is of importance, because it demonstrates that a single-shot TAP technique can produce effective analgesia for up to 2 days. The reasons for this prolonged duration of analgesia are related to the relatively poor vascularization of the transverse abdominis plane. Drug clearance from that space is therefore slow. A recent meta-analysis (160) demonstrates that TAP blocks significantly improve

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Fig. 8. — Cross-section of the abdominal wall layers. The TAP block is performed by deposition of local anesthetic between the transversus abdominis muscle and the fascial layer superficial to it. Adapted from: McDonnell N. J., et al., Anaesth. Analg., 106, 186-191, 2008.
post-caesarean section analgesia for up to 24 hours in women who did not receive intrathecal morphine (ITM). No additional analgesic benefit is observed when TAP and spinal morphine are combined. Intrathecal morphine provides lower VAS-scores, opioid consumption, and longer delays before the first rescue analgesic agent administration during the first 24 hours, but at the expense of an increased incidence of side effects. Interestingly, the presence of these side effects has been shown to have a negative impact on patient satisfaction. This may have contributed to the lack of difference in overall satisfaction scores in several studies (2, 26), despite better pain relief in the intrathecal morphine groups.

**CONCLUSION**

Adequate pain relief is essential after cesarean section to promote early recovery and early maternal care for the newborn. However, there is no ‘gold standard’ for post-caesarean pain management. The number of options is large (see also Table 1). The choice between one method or the other is at least partly determined by drug availability, regional and individual preferences, resource limitations, and financial considerations. Most methods rely on opioids, supplemented with anti-inflammatory analgesic agents, nerve blocks or other adjunctive techniques. Spinal and epidural opioids appear to have a favorable efficacy and adverse-effect profile when compared with their systemic administration. Neuraxial adjuvants (particularly clonidine and, to a lesser degree, epidural neostigmine) enhance post-caesarean section analgesia with few adverse effects apart from sedation. The use of these neuraxial drugs is not yet widely spread. In addition to opioids, systemic non-opioid analgesic agents such as paracetamol, NSAIDs, ketamine, and gabapentin may add further benefit. Among the local anesthetic techniques targeting peripheral nerve afferents, the TAP block is particularly promising. It has shown excellent results in multiple randomized controlled trials. In summary, a multimodal approach is recommended whenever possible, to maximize pain relief while minimizing untoward effects.

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Catheter administration of magnesium sulphate through epidural

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