Combined spinal epidural analgesia for labor and delivery: a balanced view based on experience and literature

M. VAN de Velde

INTRODUCTION

Almost two decades have passed since French and American trials evaluated the use of spinal opioids during labor and since European randomized trials compared conventional epidural analgesia with combined spinal epidural (CSE) analgesia (19, 35, 50). CSE analgesia has gained worldwide acceptance and is becoming increasingly popular as the method of choice for labor pain relief (54, 117, 126, 134, 135, 164). Numerous (> 280 trials, performing a literature search using CSE, combined spinal epidural analgesia and labor as search terms, were identified) studies compared CSE with conventional epidural, evaluated various intrathecal drug combinations or reported on side-effects of CSE.

Obstetric anesthetists are divided when questioned on the place of CSE in labor analgesia. Whilst some authors feel it should be the technique of choice, others reserve CSE for certain indications (34, 80, 129, 131, 141, 142). Recently, SIMMONS et al. published a Cochrane review concluding that CSE offers little benefit as compared to conventional epidural analgesia (151). However, the authors of this meta-analysis did acknowledge that CSE produced faster analgesia, resulted in less need for rescue analgesia and was associated with less urinary retention. Apart from a slight increase in the incidence of pruritus, these beneficial effects were not associated with more complications. In this authors opinion the three demonstrated benefits of CSE are sufficient to promotes it’s use if the side-effect profile remains unaltered. Furthermore it must be stressed that this Cochrane review can be criticized. Firstly, a number of well performed studies were excluded from analysis because of uncertain reasons. Inclusion of these well performed studies into the analysis might have affected the overall conclusions. Secondly, a number of outcomes were not considered in the analysis such as one-sided analgesia, epidural catheter reliability, anesthetist intervention rate, local anesthetic consumption and the occurrence of fetal heart rate abnormalities. Finally, very different types of CSE were used in the various studies. They were all considered to be a generic procedure and analyzed together.

This manuscript reviews the available literature, including those trials that were ignored by the Cochrane review, and draws conclusions regarding the place of CSE in the management of labor pain. This review will evaluate efficacy and safety of CSE and make comparisons with conventional epidural analgesia, advise on the ideal spinal drug combination and give recommendations regarding maintenance of epidural analgesia once the spinal component wears off.

CHARACTERISTICS OF LABOR PAIN RELIEF: CSE VS CONVENTIONAL EPIDURAL

Onset time of analgesia

Arguably, the most obvious advantage of the CSE technique is the rapid and spectacular onset of effective analgesia with minute concentrations of local anesthetics with or without adjuvant drugs (151). Consistently, effective labor analgesia is accomplished within 4-6 minutes following the intrathecal injection of drugs (1, 19, 35, 36, 37, 58, 73, 74, 104, 121, 152, 159, 162, 166, 167) (Fig. 1). Following conventional epidural analgesia, initial analgesia is usually achieved within 15 to 25 minutes. Some detractors argue that conventional

M. VAN de Velde, M.D., Ph.D.
Department of Anesthesiology, University Hospitals Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium.
Correspondence address: Marc Van de Velde, Director Obstetric Anesthesia and Extra Muros Anesthesia, Department of Anesthesiology, University Hospitals Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Tel.: 0032-16 34 42 70. Fax: 0032-16 34 42 45. E-mail: marc.vandervelde@uz.kuleuven.ac.be

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Epidural analgesia provides equally fast analgesia (104).

It is important to note, however, that although the onset time of epidural analgesia might be reasonable, the reported values are means. With epidural analgesia, a wide inter-patient variability exists with respect to onset time of analgesia, depending on parity, stage of labor and other relevant obstetrical and non-obstetrical factors. Especially during late labor, analgesia following an epidural injection is often delayed, and only successful if large doses are administered. With CSE, onset time is short in all patients irrespective of the stage of labor and other factors. The dose of local anesthetic only needs slight increases when labor is significantly advanced.

**Quality of pain relief: VAS scores, satisfaction and anesthetist intervention rate**

Several trials demonstrated lower VAS scores for labor pain with CSE as compared to epidural analgesia (36, 62, 77, 154). However, other comparative trials could not demonstrate a difference in VAS scores for pain (69, 104, 132). No trials report higher VAS scores with CSE. Most likely, especially during the first 30 to 60 minutes, VAS scores are lower when patients receive CSE.

Most anesthesiologists would agree that CSE provides better quality analgesia throughout the course of labor (84). Vernis and co-workers demonstrated that less patients reported unilateral analgesia with CSE as compared to conventional epidural analgesia (167). Interestingly, Hess et al. investigated the factors associated with breakthrough pain during neuraxial labor analgesia and found that patients treated with conventional epidural analgesia were three times as likely to experience recurrent breakthrough pain as compared to CSE treated women (71). However, Goodman et al., in a prospective study, failed to corroborate the latter study (62). These authors noted that additional top-ups to treat breakthrough pain were requested by similar numbers of patients irrespective of the analgesic strategy used (62).

The presence of a dural puncture may facilitate the passage of epidurally administered drugs during maintenance of analgesia to the cerebrospinal fluid. Such an effect has been reported, at least in animals (155). In patients, Leighton et al. also reported that epidural bupivacaine blocked more dermatomes when administered following an initial dural puncture as compared to epidural bupivacaine administered without prior dural puncture (87). Leighton et al. used a 24 and 27G spinal needle. Cappiello and co-workers performed a study in which the dura was perforated with a 25G Whitacre needle, without any administration of spinal drugs (22). The control group had no dural puncture. In both groups, analgesia was initiated with an epidural local anesthetic/opioid mixture. Patients treated with a dural puncture had better sacral spread, shorter onset of analgesia and better quality pain relief. Thomas et al. performed a similar study using a 27G Whitacre needle and could not find a difference between patients treated with or without a dural puncture (156). Therefore, spinal needle size may be important.

Many studies report higher patient satisfaction with CSE (36, 37, 47, 162), while no studies report on the opposite.

**Local anesthetic consumption**

Despite similar or improved quality of analgesia, local anesthetic requirements are significantly reduced with CSE as compared to low dose conventional epidural techniques (36, 37, 77, 162, 167). Discussion remains whether this is the result of the omission of the initial epidural bolus or whether a
dose sparing effect also persists during labor. The presence of the dural whole and the facilitated passage of epidurally administered local anesthetics could offer part of the explanation.

**Duration of initial analgesia**

Duration of initial spinal analgesia is usually similar to the duration of an initial epidural bolus (69, 104, 162). Spinal analgesia typically lasts for 90-150 minutes, but a wide variety exists, depending on the administered spinal drugs and on pain modulating factors such as parity, stage of labor, speed of labor, etc... (19, 27, 43, 49, 73, 95, 116, 118, 150, 168). In ideal circumstances and using multi-drug combinations, spinal analgesia may last for more than 4 hours (43, 116). Several authors continue the search for long lasting spinal analgesia, hoping that single shot spinal analgesia would ultimately be achieved. Despite extensive research, disappointingly, no more (and often less) than 50% of patients deliver during the initial spinal analgesia (168).

**Epidural catheter reliability**

Following initial spinal analgesia, bilateral analgesia and sensory changes occur, rendering the testing of the epidural catheter difficult. Hence, one may question about the reliability of the catheter to achieve bilateral analgesia once the spinal dose has worn off. However, several investigators noted that the reliability of epidural catheters following CSE is similar or better than stand alone epidural catheters (22, 38, 86, 98, 107, 109, 156, 161) (Table 1). They showed less need for epidural catheter replacement and less unilateral analgesia requiring catheter manipulation. Lee et al. reported less catheter failure at the time of topping up for Cesarean section when the catheter was placed as part of a CSE technique for labor analgesia (86).

When using a CSE technique, a perfect midline approach is required to identify the subarachnoid space and, consequently, more epidural catheters are reliably positioned into the epidural space (161). Thomas et al. interestingly noted that, when no cerebrospinal fluid was obtained following attempted CSE, much more epidural catheters required replacement subsequently, as compared to those catheters placed when cerebrospinal fluid was noted (156).

**Failed spinal component**

Failure to identify the spinal space and produce good spinal analgesia is reported in 0-18% of patients (156). As with every technique, failure may occur, but, in these instances, the epidural catheter can still be used to provide analgesia. Failure of the spinal component indicates that the epidural needle is not perfectly situated on the midline and is a risk factor for subsequent epidural catheter failure (156). In this case, re-positioning of the epidural needle is advocated by this author.

**Complications of labor analgesia : CSE analgesia vs conventional epidural analgesia**

**Pruritus**

This is the most common side effect of intrathecal opioids, occurring in almost all patients, if directly questioned (36, 98, 162, 167). In the most recent Cochrane review, pruritus was reported more frequently following CSE and was reported to be the only complication occurring more frequently than with conventional epidural analgesia (152). It usually develops shortly after analgesia. It is mild and hardly ever requires antipruritic therapy. Prophylactic ondansetron is ineffective to reduce the incidence or severity of opioid induced pruritus (169). Opioid induced itching is dose-dependent and can be modulated by other adjuvant drugs such as epinephrine (12, 19). Since patients hardly ever require therapy and seldom report pruritus as a reason for dissatisfaction, pruritus is not a reason to refrain the use of CSE and intrathecal opioids.

**Nausea**

Nausea and vomiting are very rare complications during CSE and conventional epidural

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**Table 1**

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<thead>
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<th></th>
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</tr>
<tr>
<td>Thomas 2005 (156)</td>
<td>9.3%</td>
<td>8.0% *</td>
</tr>
<tr>
<td>Capello 2008 (22)</td>
<td>3%</td>
<td>13%</td>
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<tr>
<td>Lee 2009 (86)</td>
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<td>6%</td>
</tr>
<tr>
<td>Miro 2008 (98)</td>
<td>3.4%</td>
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* Thomas et al. reported more catheter replacement when the spinal component failed (22.2%).
analgesia. No differences in the incidence of nausea have been reported when comparing the two techniques, except in the retrospective trial by Miro et al. who reported more nausea and vomiting in pregnant women treated with epidural analgesia (98). We must remember that nausea is a part of the birth process especially during induced labour.

Hypotension

As with any neuraxial technique, hypotension can occur following labour analgesia. Both CSE and conventional epidural analgesia have been associated with usually mild hypotension, which is easily treated (110). Both Ropaël et al. and Van de Velde et al. reported a high incidence of hypotension following CSE using a combination of local anaesthetics and opioids (139, 162). Hypotension following the spinal injection is transient and occurs within the first 30 minutes following initiation of analgesia (99, 149, 167). In that respect, it is important to avoid the supine position. We always keep our patients in the completely left lateral decubitus position to avoid any effect of aortacaval compression.

Hypotension occurs due to sympathetic blockade, alleviation of pain and perhaps because incorrect baseline values are used as reference (13). Indeed, if the blood pressure that immediately precedes the block is considered as the baseline value, the diagnosis of hypotension may be made inappropriately. Pain and discomfort induce hypertension and cloud the issue. Therefore, various authors recommend the use of the prenatal blood pressure as the baseline value.

Although opioids do not produce sympatholyis, hypotension is observed with pure intrathecal opioid analgesia (26, 91, 102, 138). When local anaesthetics are combined, hypotension seems to be more pronounced, but is usually easily treated (102). Intrathecal clonidine, however, is often associated with severe hypotension and this author cannot recommend it’s routine use, based on his personal experience. Hypotension can be severe and is often protracted, requiring prolonged supportive vasopressor therapy (27, 125).

Respiratory depression

Respiratory depression is a recognized complication of intrathecal opioids during labor, probably as a result of rostral spread. Several case reports have demonstrated that lipid soluble opioids may induce this potentially life threatening complication (10, 52, 63, 67, 73, 76, 90, 120, 124). In some, but not all cases, respiratory arrest can occur in relatively short stature women who received parenteral or epidural opioids prior to the spinal injection. Fortunately, respiratory depression typically occurs within the first 30 minutes and is easily reversed using naloxone. However, chest compressions and resuscitation may be required (124). Ferrouz et al. performed a retrospective chart analysis and reported 1 respiratory arrest in over 5000 CSE performed with 10 µg spinal sufentanil (52). As this complication is rare, most authors advocate vigilance and advise to use lower doses of intrathecal opioids than those initially used on empirical grounds (5).

Other complications related to excessive rostral spread of opioids and local anaesthetics have been described and include: aphonha, aphagia, dysphagia, altered levels of consciousness, high sensory block, transient swallowing difficulties, etc... (32, 41, 53, 65, 83, 145). Sudden hypoglycaemia has also been described (40, 78).

Central nervous system infections

Some authorities claim that the risk of central nervous system infections is increased secondary to the breach of the dura (16). However, Camann and Birnbach both agree that, at the moment, there is no scientific evidence indicating that CSE analgesia is associated with more infectious problems than epidural analgesia (13, 20). Indeed, several case reports of meningitis or epidural abscess have been reported following CSE anesthesia in obstetric patients (7, 15, 25, 66, 128, 167), but also after simple spinal anesthesia and conventional epidural techniques (11, 45, 103, 136). Despite these occasional case reports, CNS infections remain extremely rare, irrespective of the neuraxial technique used. Six publications evaluate the risk of infections following neuraxial anesthesia in obstetric patients (5, 39, 68, 119, 123, 146). In over 900,000 patients, only 2 cases of epidural abscess and 3 cases of meningitis were reported. Most authors, however, agree that strict aseptic techniques are of vital importance to prevent serious infections.

Neurologic complications

As with any regional technique, the potential for nerve damage is present. Several case reports in pregnant women of damage to the conus medullaris have been reported when using CSE (137). Especially with CSE, it is imperative to perform the block as low as possible, as far as the conus medullaris might extend below the L2 vertebral

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body in up to 5% of parturients (24). It has been clearly demonstrated, using radiography and ultrasound, that most anesthetists, using anatomical landmarks, are 1 to 4 interspaces away from where they think to be (24, 170). Identification of the correct interspace is therefore of prime importance. Ultrasound may be useful in that respect, especially in obese patients (24).

**Post dural puncture headache (PDPH)**

Since CSE involves a dural puncture, there is a theoretical risk of postdural puncture headache (PDPH). This is a devastating complication in an otherwise healthy mother, keen on taking care for her newborn child. However, the use of small-gauge atraumatic spinal needles (26-29 G) has dramatically decreased the problem. From the available literature, it seems that PDPH occurs in no more than 1% of patients. Furthermore, the incidence is not increased as compared to conventional epidural analgesia (13, 36, 38, 47, 84, 91, 98, 100, 109, 110, 160, 161, 167). Norris et al. reported that unintended dural puncture with the epidural needle occurs much more frequently when using conventional epidural analgesia as compared to CSE (110). Rarely, the spinal needle itself is responsible for PDPH. Usually, a dural tap with either the Tuohy needle or the epidural catheter causes postural headache. It is also worthwhile to mention several reports advising to insert the epidural catheter in the subarachnoid space following an accidental dural tap. The incidence of PDPH and bloodpatching seems to be reduced when the epidural catheter is threaded intrathecally (30, 111, 143, 148, 160).

Of interest is that air should be replaced by saline in the loss of resistance technique, as air might cause more PDPH, increase its severity and induce other problems with the epidural block, such as recurrent breakthrough pain (3, 88).

**Motor block**

For many years, strategies to reduce the incidence and severity of motor block, associated with epidural analgesia, have been designed. Lower concentrations of local anesthetic solutions, the addition of opioids and other adjuvant drugs, the introduction of patient controlled epidural analgesia and the use of newer local anesthetic agents have been instrumental in reducing problematic motor block. Low dose epidurals are successfully used to allow laboring women to maintain mobility whilst being completely pain free (37, 100). With CSE, it is easier to provide effective analgesia with no or very minute doses of local anesthetics. As already described, CSE decreases the total local anesthetic consumption (36, 37, 162) and decreases the occurrence of motor block when compared to a standard epidural technique (36, 37, 100, 162).

Some authors have questioned about the safety of walking during labor and neuraxial analgesia. However, several authors demonstrated that, with CSE, motor function and balance remains intact, whilst low dose epidurals induce clinically detectable dorsal column deficits (17, 44, 127). Ambulation became common practice and can be advised, provided that adequate precautions, written protocols and testing of motor function following initiation of analgesia are undertaken. Motor function testing is straightforward and includes the ability to perform a deep unassisted knee bend and to perform a straight leg lift for 30 seconds with the eyes closed. It remains unclear how epidural maintenance of analgesia affects postural stability and motor function (44).

Caution is required when using epidural test doses following insertion of an epidural catheter, since test doses can significantly impair motor strength (31). Controversy also exists on the effects of spinally administered epinephrine (64, 166) on the motor block. Whilst minute doses do not impair motor function, larger doses have a significant impact. A small dose of intrathecal epinephrine conveys clinical benefits in terms of prolonged spinal analgesia (64, 166).

Although reduced motor block and ambulation during neuraxial analgesia are certainly feasible, controversy concerning the benefits of ambulation remains (17, 51). Several trials demonstrated that ambulation during labor does not affect the outcome of labor (100), whilst others did note a beneficial effect. In patients without epidural analgesia, ambulation halved the operative delivery rate (4). Ambulation also reduced the length of the second stage of labor (60). In the COMET trial, mobile techniques of labor analgesia were associated with an improved labor outcome (37, 38). Despite this controversy, those women actually using ambulation during labor prefer ambulation, as it increases their feelings of self control. It was also noted that epidural top-ups administered during ambulation induced less hypotension than top-ups administered in the supine position (8).

**Progress and outcome of labor**

Epidural analgesia has been implicated in prolonged labors, in increased instrumental delivery
rate and in increased Cesarean section rate. Extensive research has now led to unanimous consensus that epidural analgesia does not produce more instrumental vaginal and operative deliveries. However, epidural analgesia prolongs the duration of the first stage of labor and increases the need for exogenous oxytocin.

Tseng et al. demonstrated in a prospective, randomized trial that CSE is associated with an increased cervical dilation rate. Patients randomized to CSE analgesia experienced a doubling of the mean cervical dilation rate and a reduced duration of the first stage of labor as compared to epidural analgesia (157). Several mechanisms have been proposed to explain these observations. First, CSE rapidly reduces epinephrine plasma levels. Since epinephrine is tocolytic (147), CSE quickly enhances uterine activity. Since analgesia and plasma epinephrine lowering occur much more rapidly than with conventional epidural analgesia, progression of labor could be enhanced. Second, since high doses of local anesthetics are avoided with CSE, the in vitro and in vivo observations that bupivacaine impairs uterine activity are also avoided (74, 171). Disappointingly, several randomized trials comparing CSE with conventional epidural analgesia could not demonstrate a difference in labor duration (37, 109, 159, 162).

As compared with low dose epidural strategies, CSE was not associated with an increased spontaneous vaginal delivery rate in most trials (36, 37, 47, 109, 132, 159, 162). Only one trial reported less instrumental vaginal deliveries with CSE than with epidural analgesia (100).

Fetal heart rate changes

Abnormal fetal heart rate recordings and fetal bradycardia are worrisome side effects that may follow any type of effective labor analgesia. Wong et al. reported more abnormal cardiocographic readings following CSE as compared to systemic analgesia (173). Some authors reported that this complication could be more common following intrathecal opioids than following conventional epidural analgesia (28, 29, 72, 79). Clarke et al. were the first to describe in detail the association between intrathecal opioids, uterine hyperactivity and fetal bradycardia in the absence of maternal hypotension (28). Since then, several non-randomized trials have evaluated the incidence of fetal heart rate changes following either intrathecal opioids or conventional epidural analgesia (106, 122, 161, 163). Nielsen et al. and Eberle et al. did not observe an increased incidence of fetal heart rate abnormalities, whilst all other non-randomised reports noted at least a doubling of the incidence of worrisome fetal heart rate changes (5) (Table 2).

Mardrosoff et al. performed a meta analysis of several prospective trials comparing intrathecal opioid analgesia with non-intrathecal opioid analgesia, with respect to fetal bradycardia (93). These authors concluded that intrathecal opioids were associated with significantly more fetal heart rate abnormalities. Vercauteren suggested that the incidence of fetal bradycardia depended on the dose of the intrathecal opioid (165). Van de Velde et al. performed a prospective, randomized trial that was specifically designed to evaluate the effects of intrathecal opioids on the incidence of worrisome fetal heart rate changes (162). These authors concluded that high doses of intrathecal opioids increased the incidence of fetal heart rate abnormalities despite a reduced incidence of hypotension. Similar results were published by Nicolet et al. (105). These authors also indicated that older age and higher VAS scores prior to analgesia were risk factors of fetal heart rate abnormalities after CSE. Gaisser suggested that the risk of fetal heart rate abnormalities is increased when the fetal head is not engaged or when decelerations are already present prior to the initiation of analgesia (56).

The presumed mechanism of opioid induced non-reassuring fetal heart rate tracings is uterine hyperactivity caused by a rapid onset analgesia and, as a result, a rapid decrease in maternal circulating catecholamines. Based on laboratory investigations by Segal et al., increased myometrical tone and increased uterine vascular resistance may be caused by the decrease of epinephrine levels in the continuing presence of high norepinephrine levels when CSE analgesia is performed (26, 147). Abrao et al. recently measured uterine tone using an intruterine pressure catheter following either CSE or conventional epidural analgesia (2). Fetal heart rate changes and uterine hypertonus occurred more

Table 2

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<th>Study</th>
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<th>Conventional epidural</th>
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<td>Nielsen 1996 (106)</td>
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<td>3.9%</td>
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<td>Kahn 1998 (75)</td>
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<td>Palmer 1999 (122)</td>
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<td>6%</td>
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<tr>
<td>Van de Velde 2001 (163)</td>
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frequently following CSE. Analgesia was initiated rather late during labor and, unfortunately, these authors only measured intrauterine tone and fetal heart rate for 15 minutes after the initiation of analgesia. Therefore, some changes associated with epidural analgesia might have been missed. They also demonstrated that the faster and the more pronounced the analgesia, the higher the probability of abnormal cardiotocographic readings. Of course, this effect is strengthened by the simultaneous occurrence of maternal hypotension in some patients.

Further study of the involved mechanism seems therefore to be required. Other mechanisms, such as direct central effects of sufentanil, are possibly involved. We can only speculate about alternative pathophysiological mechanisms. Maternal rostral spread of spinal opioids may centrally affect the release of oxytocin and subsequently induce uterine hyperactivity. It is known that intravenous opioids have central effects and alter the release of various central peptides, including oxytocin and vasopressin (140). In a recent interesting paper, Stocche et al. studied the release of oxytocin in women during the first stage labor and undergoing regional analgesia (153). They compared conventional epidural analgesia using plain bupivacaine 0.25% with intrathecal sufentanil 10 µg and measured maternal plasma oxytocin levels at 15, 30, 60 and 90 minutes after induction of analgesia. Intrathecal sufentanil decreased the plasma concentration of oxytocin. These results are in contradiction with the hypothesis that spinal opioids may induce uterine hyperactivity by modulating central oxytocin release. However, the authors themselves admit they only infrequently sampled blood. As oxytocin release typically occurs in spurts, has an extremely short plasma half-life and as the authors only performed their first sampling after 15 minutes, they may have missed an initial increase in oxytocin release followed by the observed decrease in plasma oxytocin. More work is therefore required to elucidate the mechanism responsible for uterine hyperactivity and fetal bradycardia occurring after intrathecal opioids.

It is important to note that neonatal and obstetric outcome is not affected by the use of intrathecal opioids. Carvalho et al. failed to demonstrate any changes in fetal oxygen saturation following CSE analgesia (23). In none of the reports, emergent C-sections had to be performed as a result of sufentanil-induced non-reassuring fetal heart rate tracings (2, 48, 75, 93, 106, 122, 162, 163, 166). In addition, neonatal outcome, as assessed by Apgar scores, umbilical artery pH and admittance to the neonatal intensive care, was unaffected by the technique used. Albright and Forster performed an institutional retrospective survey involving 2500 patient records and observed no increase in emergency Cesarean deliveries associated to the use of intrathecal opioids (6). Only Gambling et al. contradicted this and reported an increased C-section rate due to more non-reassuring fetal heart rate abnormalities (57). However, also in their study, neonatal outcome was good and not different from the epidural group.

**TESTING THE EPIDURAL CATHETER FOLLOWING CSE**

Since epidural catheters can inadvertently be misplaced in either the cerebrospinal fluid or in an epidural vein, anesthetists have been using test doses to verify the correct position of the catheter. Unfortunately, test doses are neither sensitive nor specific (33, 108). Furthermore, epinephrine containing test doses can induce motor impairment and thus complicate ambulation during labor (31). Some authors also suggested that an epinephrine containing test dose has potential adverse effects on uteroplacental perfusion (92). As a result, several authors suggested to abandon routine testing of the epidural catheter, since adequate analgesia confirms the correct position of the catheter without prior testing (14).

With CSE, analgesia occurs rapidly and testing the functionality of the epidural catheter is not possible until the initial spinal dose wears off. Many authors consider the fact that the reliability of the epidural catheter is uncertain during this period as a major disadvantage. Their concern is related to the possibility that the catheter may be dysfunctional when an emergency cesarean section is required. Especially in high risk pregnancies, this is considered a major drawback. However, it is important to note that, even with a well tested epidural catheter, we can never be absolutely sure that, several hours later, the catheter remains correctly positioned. Even with conventional epidural catheters, fractioned dosing or a de novo test dose are required when the catheter is used for the injection of high doses of local anesthetics.

A second concern involves the fact that some authors do not want to initiate epidural analgesia immediately after the spinal dose. Only when the epidural catheter is formally tested, once the spinal dose has worn off, the catheter is used throughout labor. As a result, most patients will experience
breakthrough pain. However, several authors initiate an epidural infusion immediately after the initial spinal dose (55). With low volume, low dose techniques, the risk of total spinal anesthesia or toxic side effects is minimal. These doses cannot produce systemic toxicity or total spinal anesthesia even when direct intravascular or intrathecal injection occurs. However, if a continuous epidural infusion or patient controlled epidural analgesia does not produce adequate analgesia, one must consider an intravascular position of the catheter.

**INTRATHecal DRUG COMBINATIONS**

**Local anesthetics**

Currently, the most frequently used local anesthetic agent for intrathecal labor analgesia is bupivacaine, usually in combination with opioids. Levobupivacaine and ropivacaine have also been used successfully. Lim et al. compared 2.5 mg bupivacaine with 2.5 mg ropivacaine and 2.5 mg levobupivacaine (89). Bupivacaine produced the longest analgesia but the highest incidence of motor block. These results were not confirmed by Sah et al. who did not find a difference between levobupivacaine and bupivacaine (144). Camorcia and coworkers described the minimum local analgesic doses of all three local anesthetics and suggested a potency hierarchy of spinal bupivacaine > levobupivacaine > ropivacaine (21). Whitty et al. described the ED95 of spinal bupivacaine combined with fentanyl (170). Van de Velde et al. were the first to construct the full dose response relationship of spinal ropivacaine, levobupivacaine and bupivacaine combined with opioids for labor analgesia. Contrary to Camorcia et al., these investigators noted that bupivacaine was significantly more potent then both other local anesthetics and that ropivacaine and levobupivacaine were of similar potency (158).

**Opioids**

Plain intrathecal opioids are efficient at producing labour analgesia. Palmer et al. established that 25 µg fentanyl was the optimal intrathecal dose (121). Increasing the dose above 25 µg did not improve the duration or quality of analgesia, but increased the incidence of side effects. For sufentanil, an ED95 of 8.9 µg was established (70). However, certainly in Europe, most anaesthesiologist prefer the intrathecal combination of local anaesthetics and opioids. Adding opioids to the spinal mixture reduces the ED95 of the local anesthetic agent and dose-dependently prolongs the duration of the initial spinal analgesia (154). Therefore, most authors recommend a local anesthetic/opioid combination in this indication. Wong et al. showed that 15 µg fentanyl added to the local anesthetic/opioid mixture was the optimal dose in terms of efficacy and side-effects (172).

Patients may react very differently to intrathecal opioids. Landau et al. demonstrated that mu-opioid receptor genetic variants influence the dose required to produce effective analgesia (85) (already described above). Respiratory depression following intrathecal opioids has been described. This occurred usually in small patients receiving high doses of opioids following initial parenteral opioid analgesia. Respiratory depression occurred within 30 minutes from injection. Vigilance following the intrathecal injection of opioids is therefore required. During labour analgesia, intrathecal opioids have been associated with new onset foetal heart rate changes (28, 162). Usually these changes were related to uterine hyperactivity and not maternal hypotension. Several authors postulated that an imbalance between maternal catecholamines following rapid spinal analgesia produces uterine hypertonicity. It remains unclear why this only occurs following high dose intrathecal opioids and not following the combination of lower doses of opioids and local anaesthetics (162).

**Clonidine**

Chiari et al. studied the use of pure spinal clonidine for labour analgesia (27). This seems not feasible since doses producing adequate analgesia also induce unacceptable side effects such as hypotension. Adding lower doses of clonidine (15-45 µg) to spinal analgesics does improve the duration and quality of the initial spinal analgesia (9, 95, 96, 118). However, especially when clonidine is combined with local anaesthetic agents, significant and prolonged hypotension is likely to occur (9, 96, 118, 125).

**Epinephrine**

Epidurally administered epinephrine significantly reduces the MLAC of bupivacaine in labouring patients and improves the quality of analgesia (130). Also for spinal use, epinephrine, combined with local anaesthetics and opioids, has been evaluated in a wide range of doses from 2.25-
100 µg. Duration of intrathecal analgesia was consistently prolonged (58, 64).

Unfortunately, epinephrine also induces an increased incidence of maternal motor deficit, especially when administered epidurally or intrathecally (31, 61). Vercauteren, however, reported that minute doses (2.25 µg) of spinal epinephrine were not associated with more motor block (166). This was confirmed by Gurbet and co-workers (64). Epidural epinephrine might also prolong labour duration through β-agonist effects, especially when higher doses are infused in the epidural space (46, 112, 115). Furthermore, adding epinephrine to pharmacist-prepared solutions complicates storage and significantly increases the price of handling and preparation. Thus, this author has abandoned the addition of epinephrine to the local anaesthetic solution used for spinal and epidural administration.

Neostigmine

NELSON et al. investigated the analgesic potential and side effect profile of 5, 10, 20 µg intrathecal neostigmine alone (101). From this first phase study, these investigators chose 10 µg as the optimal dose to be added to intrathecal sufentanil and determined the ED₅₀ of spinal sufentanil with and without neostigmine. Neostigmine successfully reduced the ED₅₀ of spinal sufentanil. In a further step, they compared twice the ED₅₀ of spinal sufentanil with neostigmine to twice the ED₅₀ of plain spinal sufentanil. A synergistic effect on the duration of neostigmine-induced analgesia was observed. D’ANGELO et al., however, reported no increase in analgesic duration with neostigmine as a part of a multi-drug combination (local anaesthetic, opioid, clonidine and neostigmine) (42). Furthermore, several authors reported a very high incidence of severe nausea and vomiting (116).

Other drugs: magnesium and adenosine

Both adenosine and magnesium have been added to intrathecal opioids to relieve labour pain (18, 133). No significant advantages of adding adenosine to the analgesic mixture were observed. Magnesium prolonged intrathecal fentanyl analgesia.

Maintenance of epidural analgesia following the initial spinal dose

OKUTOMI et al. studied the optimal moment to initiate a continuous epidural infusion following the initial spinal dose (114). These authors suggested to start the infusion early, within 30 minutes of the spinal dose, to avoid breakthrough pain. MISSANT et al. studied patient-controlled epidural analgesia (PCEA) with or without a continuous epidural infusion. They concluded that a background infusion resulted in less breakthrough pain, less anesthetist interventions and less local anesthetic consumption (97). OKUTOMI et al. recently confirmed these findings with a slightly higher background infusion (113).

General conclusions

CSE analgesia is a very popular technique for labor pain relief. A recent Cochrane review suggests that CSE produces much faster analgesia than conventional epidural analgesia. Although various authors limit the use of the technique to specific indications, a wide variety of indications has been described by different authors. As a result, almost all patients fall in one of these categories. CSE analgesia provides rapid, highly effective analgesia with

| Table 3 |
|--------------------------|-----------------|-----------------|-----------------|
| Suggested drug combinations for intrathecal use to initiate CSE labour analgesia. Dose may vary according to the stage of labour and intensity of labour pain |
| | Local anesthetic (mg) | Opioid (µg) | Volume (mL) |
| Suggestion 1 | Bupivacaine 2.5-3.5 mg | Sufentanil 1.5-2.5 µg | 2-3 mL |
| Suggestion 2 | Bupivacaine 2.5-3.5 mg | Sufentanil 1.5-2.5 µg | 2-3 mL |
| Suggestion 3 | Levobupivacaine 3.5-4.5 mg | Fentanyl 10-15 µg | 2-3 mL |
| Suggestion 4 | Levobupivacaine 3.5-4.5 mg | Sufentanil 1.5-2.5 µg | 2-3 mL |
| Suggestion 5 | Ropivacaine 3.5-4.5 mg | Fentanyl 10-15 µg | 2-3 mL |
| Suggestion 6 | Ropivacaine 3.5-4.5 mg | Fentanyl 10-15 µg | 2-3 mL |

These are just suggestions based on literature evidence and personal experience from the author.
minimal motor block, reduced local anesthetic
doses and perhaps an improved obstetric outcome.
Maternal satisfaction is improved. An important
advantage of the CSE technique is the enhanced
doses and perhaps an improved obstetric outcome.
epidural catheter reliability. PDPH and infections
do not occur more frequently than with convention-
al epidural analgesia. Non reassuring fetal heart rate
tracings occur significantly more frequently follow-
ing high doses of intrathecal opioids. Occasionally,
respiratory depression, following high doses of
intrathecal opioids, can occur.

This author strongly recommends using CSE
as the standard technique of labor analgesia.

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