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Review

Modern neuraxial labor analgesia: options for initiation, maintenance and drug selection

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Most authors would agree that central neuraxial analgesia is the best form to manage labor pain. When neuraxial analgesia is administered to the parturient in labor, different management choices must be made by the anesthetist: how will we initiate analgesia, how will analgesia be maintained, which local anesthetic will we use for neuraxial analgesia and which adjuvant drugs will we combine? The present manuscript tries to review the literature to answer these questions.

INITIATION OF NEURAXIAL ANALGESIA

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 *(1–3)*. CSE analgesia has gained worldwide acceptance and is becoming increasingly popular as the method of choice for labor pain relief *(4–9)*. 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 *(10–15)*. Recently, Simmons et al. published a Cochrane review concluding that CSE offers little benefit as compared to conventional epidural analgesia *(16)*. 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. 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 abnormalities. Finally, very different types of CSE were used in the various studies. They were all considered to be a generic procedure and analyzed combined.

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 *(16)*. Consistently, effective labor analgesia is accomplished within 4–6 minutes

following intrathecal injection *(1, 2, 17–29)*. Following conventional epidural analgesia, initial analgesia is usually achieved between 15 and 25 minutes. Some detractors argue that conventional epidural analgesia provides equally fast analgesia *(23)*. 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 depending on parity, stage of labor and other relevant obstetric 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.

Several trials demonstrated lower VAS scores for labor pain with CSE as compared to epidural analgesia *(18, 30–32)*. However, other comparative trials could not demonstrate a difference in VAS scores for pain *(23, 33, 34)*. No trials report higher VAS scores with CSE. Most likely especially during the first 30 to 60 minutes VAS scores are lower when patients are treated with CSE.

Most anesthesiologists would agree that CSE provides better quality analgesia throughout the course of labor *(35)*. Vernis and co-workers demonstrated that less patients reported unilateral analgesia with CSE *(29)*. 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 *(36)*. In contrast however, Goodman *et al.* in a prospective study noted that additional top-ups to treat breakthrough pain were requested by similar numbers of patients irrespective of the analgesic strategy used *(37)*.

The presence of a dural puncture may facilitate the passage of epidurally administered drugs during maintenance of analgesia to the cerebrospinal fluid. At least in animals such an effect has been reported *(38)*. 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 *(39)*. Leighton *et al*. used a 24 and 27G spinal needle. Cappiello and co-workers performed a randomized, double-blind study in which the dura was perforated with a 25G Whitacre needle without administration of spinal drugs *(40)*. The control group had no dural puncture. 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 *(41)*. So spinal needle size may be important. Many studies report higher patient satisfaction with CSE *(18, 19, 27, 42)*, while no studies report on the opposite.

Despite similar or improved quality of analgesia, local anesthetic requirements are significantly reduced with CSE *(18, 19, 27, 29*). Discussion remains whether this is the result of the omission of the initial epidural bolus or that also during labor a dose sparing effect persists. The presence of the dural whole and the facilitated passage of epidurally administered local anesthetics could offer part of the explanation.

Following initial spinal analgesia, bilateral analgesia and sensory changes occur, making testing of the epidural catheter difficult. The epidural catheter cannot prove itself and many may question the reliability of the catheter to achieve bilateral analgesia once the spinal dose is worn off. However various investigators noted that the reliability of epidural catheters following CSE was significantly increased as compared to stand alone epidural catheters *(40, 41, 43–48)* (Table 1). There was less need for epidural catheter replacement and there was less unilateral analgesia requiring catheter manipulation. Lee et al. reported less catheter failure when topping up for Cesarean section when the catheter was placed as part of a CSE technique of labor analgesia *(44)*.

When using a CSE technique, a perfect midline approach is required to identify the subarachnoid space and consequently more epidural catheters reliably are positioned into the epidural space *(48)*. Thomas et al. interestingly noted that when no cerebrospinal fluid was obtained following attempted CSE, subsequently much more epidural catheters required replacement as compared to those catheters placed when cerebrospinal fluid was noted *(41)*.

The CSE technique may have more complications. What does the literature tells us? Pruritus is the most common side effect of intrathecal opioids, occurring in almost all patients, if directly questioned *(18, 27, 29, 45)*. In the most recent Cochrane review, pruritus was more frequent following CSE and was reported to be the online complication occurring more frequent as compared with conventional epidural analgesia *(16)*. It usually develops shortly after analgesia. It is mild and hardly ever requires antipruritic therapy. Since patients hardly ever require therapy and seldom report pruritus as a reason for dissatisfaction, pruritus is no reason to refrain from using CSE and intrathecal opioids.

TABLE 1

Reliability of epidural catheters: % of failed epidural catheters not producing adequate analgesia and that were resited.

	CSE	Epidural
Norris 2000 *(46)*	0.2 %	1.3 %
COMET 2001 *(43)*	4.0 %	6.8 %
Van de Velde 2001 *(48)*	1.49 %	3.18 %
Thomas 2005 *(41)*	9.3 %	8.0 %*
Cappiello 2008 *(40)*	3 %	13 %
Lee 2009 *(44)*	1 %	6 %
Miro 2008 *(45)*	3.4 %	6.2 %

* Thomas *et al.* reported more catheter replacement when the spinal component failed (22.2%).

Nausea and vomiting are very rare complications during CSE and conventional epidural analgesia. No differences in the incidence of nausea have between reported when comparing the two techniques, except in the retrospective trial by Miro *et al.* who reported more nausea and vomiting in patients treated with epidural analgesia *(45)*. We must remember that nausea is a part of the birth process especially during induced labour.

Both CSE and conventional epidural analgesia have been associated with usually mild hypotension, which is easily treated *(49)*. Hypotension following the spinal injection is transient and occurs within the first 30 minutes following initiation of analgesia *(29, 50, 51)*. In clinical, routine practice 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.

Although opioids do not produce sympatholysis, hypotension is observed with pure intrathecal opioid analgesia *(52-55)*. When local anaesthetics are combined, hypotension seems to be more pronounced, but clinically usually easily treated *(54)*. Intrathecal clonidine, however, is often associated with severe hypotension and this author can not recommend it's routine use based on his personal experience with this drug. Hypotension can be severe and is often protracted requiring prolonged supportive vasopressor therapy *(56, 57)*.

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 *(21, 58-65)*. In some, but not all, cases respiratory arrest occurred in relatively short stature women who had received parenteral or epidural opioids prior to the spinal injection. Fortunately, respiratory depression occurred typically within the first 30 minutes and was easily treated and reversed using naloxone. In one patient chest compressions and resuscitation was required *(65)*. Ferrouz *et al.* performed a retrospective chart analysis and reported 1 respiratory arrest in over 5000 CSE performed with 10 μg spinal sufentanil *(59)*. As this complication is rare, most authors advocate vigilance and advise to use lower doses of intrathecal opioids then those initially used on empirical grounds *(66)*. Other complications related to excessive rostral spread of opioids and local anaesthetics have been described and include: aphonia, aphagia, dysphagia, altered levels of consciousness, high sensory block, transient swallowin difficulties, etc… *(67–72)*. Also sudden hypoglycemia has been described *(73, 74)*.

Some authorities claim that the risk of central nervous system infections is increased secondary to the breach of the dura *(75)*. 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 *(76, 77)*. Indeed several case reports of meningitis or epidural abscess have been reported following CSE anesthesia in obstetric patients *(29, 78–82),* but also with simple spinal anesthesia and conventional epidural techniques central nervous system infections have been reported *(83–86)*. 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 *(66, 87–91)*. 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.

Several case reports in pregnant women of damage to the conus medullaris have been reported when using CSE *(92)*. Especially with CSE it is imperative to perform the block as low as possible since the conus medullaris might extend below the L2 vertebral body. Up to 5% of parturients can have a conus which extends lower than the L2 vertebral body *(93)*. To avoid conus damage, careful attention to the correct interspace is required. 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 *(93, 94)*. Identification of the correct interspace is therefore of prime importance. Ultrasound may be useful, especially in obese patients, to indetify or confirm the correct interspace *(93)*.

Since CSE includes 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 *(18, 29, 35, 42, 43, 45, 47, 49, 53, 76, 95, 96)*. Norris *et al.* reported that unintended dural puncture with the epidural needle occurs much more frequent when using conventional epidural analgesia as compared to CSE *(49)* 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 reduced when the epidural catheter is threaded intrathecally *(96–100)*. Of interest is that air should be replaced by saline in the loss of resistance technique, as air might cause more PDPH, increase it's severity and induce other problems with your epidural block such as recurrent breakthrough pain *(101, 102)*.

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 *(19, 95)*. With CSE it is easier to provide effective analgesia with no or very minute doses of local anesthetics. As already described, CSE decreased total local anesthetic consumption *(18, 19, 27)* and decreased the occurrence of motor block compared to standard epidural techniques *(18, 19, 27, 95)*.

Some authors have questioned the safety of walking during labor and neuraxial analgesia. However, several authors demonstrated that with CSE motor function and balance remained intact, whilst low dose epidurals induced clinically detectable dorsal column deficits *(82, 103, 104)*. Ambulation is become common practice and can be advised, provided adequate precautions, written protocols and testing of motor function following initiation of analgesia is performed. Motor function testing is straightforward and includes the ability to perform a deep knee bend unassisted and to perform a straight leg lift for 30 seconds with the eyes closed. Caution is required when using epidural test doses following insertion of an epidural catheter, since test doses can significantly impair motor strength *(105)*. Controversy also exists on the effects of spinally administered epinephrine *(28, 106)* on motor block. Whilst minute doses do not impair motor function, larger doses have a significant impact *(64, 106)*.

Epidural analgesia has been implicated in prolonged labors, an increased instrumental delivery rate and an 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. Tsen *et al.* demonstrated in a prospective, randomized trial that CSE is associated with an increased cervical dilation rate *(107)*. 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 *(107)*. Disappointingly, several randomized trials comparing CSE with conventional epidural analgesia could not demonstrate a difference in labor duration *(19, 26, 27, 47)*. CSE as compared with low dose epidural strategies was not associated with an increased spontaneous vaginal delivery rate in most trials *(7, 18, 19, 26, 33, 42, 47)*. Only one trial reported less instrumental vaginal deliveries with CSE as compared to epidural analgesia *(95)*.

Abnormal fetal heart rate recordings and fetal bradycardia are worrisome side effects that may follow any type of effective labor analgesia. Some authors reported that this complication could be more common following intrathecal opioids than following conventional epidural analgesia *(108–111)*. 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 *(108)*. Since then several non-randomized trials have evaluated the incidence of fetal heart rate changes following either intrathecal opioids and conventional epidural analgesia *(48, 112–114)*. 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.

Mardirossof et al. performed a meta analysis of several prospective trials comparing intrathecal opioid analgesia with non-intrathecal opioid analgesia with respect to fetal bradycardia *(115)*. 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 *(116)*. Van de Velde *et al.* concluded that high doses of intrathecal opioids increased the incidence of fetal heart rate abnormalities despite a reduced incidence of hypotension *(27)*. Similar results were published by Nicolet *et al. (117)*. These authors also indicated that older age and higher VAS scores prior to analgesia were risk factors associated with fetal heart rate abnormalities after CSE. Gaiser suggested that the risk of abnormalities in the fetal heart rate is increased when the fetal head is not engaged or when decelerations are already present prior to initiation of analgesia *(118)*.

The presumed mechanism of opioid induced non-reassuring fetal heart rate tracings is uterine hyperactivity caused by rapid analgesia and as a result a rapid decrease in maternal circulating cathecholamines. Abrao et al. recently measured uterine tone using an intrauterine epressure catheter following either CSE or conventional epidural analgesia *(119)*. Fetal heart rate changes and uterine hypertonus occurred more frequently following CSE. Analgesia was initiated rather late in labor and unfortunately these authors only measured intrauterine tone and fetal heart rate for 15 minutes after initiation of analgesia. So changes associated with epidural analgesia might have been missed. They also demonstrated that the faster analgesia occurred and the more pronounced it was, the higher the probability of abnormal cardiotocographic readings. Of course this effect is strengthened by the simultaneous occurrence of maternal hypotension in certain patients.

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 *(119)*. In none of the reports emergent C-sections had to be performed as a result of sufentanil induced non-reassuring fetal heart rate tracings *(27, 28, 112, 113, 114, 115, 118, 120, 121)*. Also 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 delivery associated to the use of intrathecal opioids *(122)*. Only Gambling *et al.* contradicted this and reported an in-

creased C-section rate due to more non-reassuring fetal heart rate abnormalities *(123)*. However also in their study neonatal outcome was good and not different from the epidural group.

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 *(124, 125)*. Furthermore epinephrine containing test doses can induce motor impairment and thus complicate ambulation during labor *(105)*. Some authors also suggested that an epinephrine containing test dose has potential adverse effects on uteroplacental perfusion *(126)*. 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 *(127)*.

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 the moment 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 following the initial spinal dose. 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.

Currently, a local anesthetic (bupivacaine, ropivacaine or levobupivacaine)/opioid (fentanyl/sufentanil) mixture is used to initiate spinal anesthesia. 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 *(128)*. These investigators noted that bupivacaine was significantly more potent then both other local anesthetics and that ropivacaine and levobupivacaine were of similar potency *(128)*. They also noted that in active labor much more local anesthetic was required then previously described on empirical grounds to produced affective analgesia in all parturients.

Several authors have suggested to prolong initial intrathecal analgesia by the addition of various other drugs such as clonidine, epinephrine and neostigmine. Although these drugs were succesfull in prolonging analgesia, they also produced significantly more side-effects.

MAINTENANCE OF ANALGESIA

Maintenance of analgesia can be achieved using either intermittent top-ups (ITU), continuous epidural infusions (CEI) or patient controlled epidural analgesia (PCEA) with or without a background infusion. In California, only 25% of obstetric anaesthesia units used PCEA in 2005 *(129)*. In the United Kingdom only 5% of units used PCEA in 1999 *(130)*. However in Belgium in 2005, the majority of hospitals used PCEA *(131)*.

The pros and cons of ITU, CEI and PCEA by comparing them to each other will be reviewed. We will evaluate quality of analgesia and incidence of unwanted side-effects of analgesia according to the mode of maintaining analgesia.

Intermittent top-ups versus continuous infusion

The administration of intermittent top-ups is historically the first modality with which epidural analgesia was maintained. Anaesthetists or midwifes administer a bolus of local anaesthetic solution either on patient request or after a fixed interval. Several potential problems however may arise. Administration of large doses of local anaesthetic in bolus can lead to systemic toxicity. Furthermore bolus administration may elicit maternal hypotension and fetal heart rate abnormalities. Additionally, ITU can lead to periods of inadequate pain control. As a result investigators tried to improve epidural analgesia by developing CEI.

Lamont et al. demonstrated that ITU are indeed associated with more additional top-ups, that hypotensive episodes are more frequent, that fetal heart rate changes occur with a higher frequency, that more babies require admission to the neonatal care unit and that quality of analgesia is less then with CEI *(132)*. Also D'Athis *et al.* showed that CEI is associated with better analgesia and less local anaesthetic consumption *(133)*. However many studies reported no differences in terms of analgesic quality between ITU and CEI *(133–135),* and some reported that ITU was associated with better analgesia *(136–137)*. Most studies *also showed that local anaesthetic consumption is reduced with ITU (133, 134, 136, 137)*. Despite less anaesthetic consumption, obstetric outcome is usually similar between the two modalities *(135–140),* except for more spontaneous deliveries with ITU in the study by Smedstad *et al. (134)*. So basically, CEI and ITU are quite similar in terms of quality of analgesia and incidence of side-effects with a tendency towards better performance for the ITU technique.

Patient controlled epidural analgesia (PCEA) versus intermittent top-ups

Several studies compared PCEA with ITU techniques of maintaining epidural analgesia during labour *(135, 137, 140–144)*. Quality of pain relief was similar between the two modalities, except in the study by Paech *et al. (143):* ITU resulted in higher maximal pain scores. Also in the study by Halonen *et al.* PCEA produced better analgesia *(141)*. Gambling et al. reported increased satisfaction scores with PCEA as compared to ITU, but other authors could not confirm these results *(144)*. In terms of local anaesthetic consumption reported results are conflicting: most studies show no difference, while some report an increased consumption with PCEA and others report a decreased consumption with PCEA *(137, 141–143)*. Two studies demonstrate a negative effect on obstetric outcome with PCEA *(141, 143)*. Paech *et al.* observed a prolonged second stage of labour, while Halonen et al. noted more Caesarean sections as well as a longer second stage *(141, 143)*.

Patient controlled epidural analgesia (PCEA) versus continuous epidural infusions (CEI)

Numerous studies have evaluated PCEA since it's introduction into obstetric analgesia in 1988 by Gambling *et al. (145)*. PCEA produced similar levels of pain relief in most studies in terms of recorded Visual Analogue Scores for pain *(135, 137, 140, 145–155)*. However, quality of pain relief is more than recorded VAS scores. One important parameter is the incidence of breakthrough pain requiring medical staff (anaesthetist) intervention. Although theoretically CEI may require fewer anaesthetist interventions, most studies indicate that just the opposite is true. PCEA is associated with less medical staff interventions. This was clearly demonstrated by *an excellent meta-analysis by van der Vyver et al. comparing PCEA with CEI (156)*. Some studies also showed that patient satisfaction was increased with the PCEA modality *(147)*. Patient satisfaction is increased because of increased patient responsibility, patient control of labour experience, patient titration to the desired level of pain and a considerable placebo effect by pressing the PCEA button.

PCEA is also associated with significantly less local anaesthetic consumption *(156)*. Reductions vary from study to study between 20% less to 55% less local anaesthetic consumption. As a result significantly less motor block is observed with PCEA *(156)*. It remains unclear whether this results in a better obstetric outcome. Most studies can not identify a difference between both modalities. However, *some indicate less outlet forceps deliveries may be required when using PCEA (148, 253, 154)*. The meta-analysis by van der Vyver *et al.* could not confirm this however *(156)*.

The use of background infusions combined with a PCEA modality is controversial. Some authors indicate that a background infusion confers no benefit while others suggest better pain scores with a background infusion *(157–159)*. However the difference may be that a background infusion seems particularly useful when analgesia is initiated with CSE. The background infusion ensures epidural priming when the patient requests the first epidural bolus. When the epidural space is primed more rapid and more effective analgesia is most likely obtained *(158, 159, 160)*.

In recent years several authors have evaluated the use of PCEA combined with automated intermittent boluses. Both Wong *et al.* and Sia *et al.* compared automated boluses with continuous background infusion both combined with PCEA *(161, 162)*. In both studies automated boluses performed better resulting in less local anaesthetic consumption, less clinician intervention and better quality of pain relief. Now, several studies are emerging looking at computer integrated PCEA. Computer integrated PCEA is a conventional PCEA system but with an automated feedback loop: the rate of a continuous background infusion is adapted according to the administered PCEA boluses during the previous hour *(163)*. Computer integrated PCEA resulted in less breakthrough pain and higher parturient satisfaction.

CONCLUSION

Based on the literature, PCEA and ITU seem to be superior options compared to CEI for maintenance of labour analgesia. Both modalities result in less local anaesthetic consumption, less motor block and increased patient satisfaction as compared to CEI. PCEA may be slightly more expensive then ITU, but results in far less medical staff workload. Depending on local legislation, ITU may not be an option. PCEA with a background infusion, especially when CSE is used, may be a good option. However te background infusion rate should be small (no more than 25% of total hourly consumption). New PCEA modalities are being developed.

Choice of local anesthetic

Bupivacaine is worldwide probably the most commonly used drug for obstetric regional anaesthesia and analgesia. Reports of bupivacaine cardiotoxicity after unintentional intravascular injection mainly in obstetric patients have led to the development of ropivacaine and levobupivacaine *(164)*. These drugs appear to be safer alternatives as compared to bupivacaine. These drugs also have a greater separation between sensory and motor blockade, an especially advantageous feature during labour analgesia. Since these drugs were marketed, the pharmaceutical industry is pushing anaesthetists to change their practice in favour of these new local anaesthetic agents. Is this the correct strategy to follow? What is the place of racemic bupivacaine in modern obstetric analgesia?

Risk of systemic toxicity

All local anaesthetics can produce systemic toxicity by direct and indirect mechanisms that derive from their

mode of local anaesthetic actions, i.e. inhibition of voltage-gated ion channels *(165, 166)*. Furthermore local anaesthetics also interfere with mitochondrial respiration by impeding oxidative phosphorylation, thus depleting the cell's energy reserve. Ropivacaine and levobupivacaine both have lower systemic toxicity then bupivacaine *(165–167)*. Ropivacaine seems to be the least toxic, levobupivacaine has intermediate toxicity and bupivacaine is most toxic. Evidence comes from numerous *in vitro* cellular studies, ex vivo whole organ studies, whole body studies in animals, whole body studies in human volunteers and case reports. Reduced systemic toxicity has also been demonstrated in pregnant animals *(168)*.

Caution remains essential in using large volumes or doses of local anaesthetic. These new local anaesthetics should not be regarded as "safe" but as "safer" alternatives to bupivacaine. It remains essential that clinicians use the customary precautions to minimize the risk of systemic toxicity e.g. standard monitoring, aspiration of the catheter prior to injection of local anaesthetics, use of a test dose, fractionation of the injected dose and use of the lowest local anaesthetic concentration feasible.

Excellent labour analgesia with minimal side-effects

One of the factors implicated in the association between epidural analgesia and increased rates of operative delivery is motor block from epidural local anaesthetic. Motor block can be minimized by reducing the concentration of local anaesthetic, by decreasing the total dose used or by choosing a local anaesthetic with a high differential sensory:motor block ratio.

Several trials have evaluated conventional labour analgesia using rather high concentrations of different local anaesthetics (≥ 0.2%). A meta-analysis of six trials compared 0.25% of ropivacaine with 0.25% bupivacaine. A total of 391 patients were analysed. The authors concluded that ropivacaine produced less motor block, resulted in a higher spontaneous vaginal delivery rate and had less effects on the neurological adaptive capacity scores (NACS) of the neonates *(169)*. Asik *et al*. produced similar results comparing 0.2% ropivacaine and bupivacaine solutions combined with fentanyl for epidural labour analgesia: less motor block and more spontaneous vaginal deliveries were noted *(170)*.

TABLE 1

Number of patients with motor block in bupivacaine or ropivacaine treated patients using similar and low (≤ 0.125%) concentrations of local anaesthetic. * $p < 0.05$ versus bupivacaine.

	Bupivacaine	Ropivacaine	Number of patients
Campbell *et al. (173)*	5	0*	40
Meister *et al. (174)*	18	8*	50
Gautier *et al. (175)*	15	3*	90
Lee *et al. (176)*	21	10	346
Owen *et al. (178)*	12	8	50
Gogarten *et al. (179)*	11	4	109
Chua *et al. (180)*	5	3	32
Fischer *et al. (181)*	19	10	189
Atienzar *et al. (177)*	18	13	65
TOTAL	124	59	971

However, modern labour analgesia uses far lower concentrations of local anaesthetics. The advantages in terms of motor block and labour outcome of lower epidural local anaesthetic concentrations were well demonstrated by the COMET trial *(171)*. Halpern and Walsh performed a meta-analysis of 23 randomised trials that compared ropivacaine and bupivacaine during labour analgesia *(172)*. Onset, duration and quality of analgesia were perfectly comparable between the two local anaesthetics. No differences in mode of delivery or other outcome parameters were identified, except for a more frequent incidence of motor block with bupivacaine. The results related to motor block were not combined statistically because of the large amount of heterogeneity among studies resulting from the large differences in drug doses and concentrations used among studies. If one outcome parameter, however, is not evaluated statistically because differences in methodology among studies, why then compare other outcome parameters despite these methodological differences among studies?

Several individual studies using low concentrations of local anaesthetic (≤ 0.125%) however did demonstrate differences in motor block with ropivacaine producing less motor block then bupivacaine *(173–181)*. Gautier et al. clearly demonstrated that, especially if the cumulative epidural dose of local anaesthetic increased, the risk of motor block was increased with bupivacaine *(175)*. This difference persisted if lower concentrations of epidural bupivacaine were used to provide analgesia. Table 1 gives an overview of motor block reported in several studies that compared low and similar concentrations of ropivacaine and bupivacaine during labour analgesia. Combined, it becomes clear that motor block occurs much less with ropivacaine. Atienzar demonstrated that both ropivacaine and levobupivacaine produced less motor block *(177)*.

This has been recently confirmed using the MLAC methodology. Lacassie et al. determined the motor block MLAC concentration of ropivacaine and bupivacaine using a model of up-and-down sequential allocation *(182)*. These authors noted that ropivacaine was significantly less potent for motor block then bupivacaine, at 66% that of bupivacaine.

Similar observations can be made for intrathecal ropivacaine and bupivacaine. Excellent analgesia is achieved with both agents using similar spinal doses but with less motor impairment in patients treated with ropivacaine. Table 2 gives an overview of the number of patients developing detectable motor block in various studies that compare intrathecal ropivacaine and bupivacaine *(183–186)*.

TABLE 2

Number of patients with motor block in bupivacaine or ropivacaine treated patients using similar doses of local anaesthetic administered intrathecally. * $p < 0.05$ versus bupivacaine.

	Bupivacaine	Ropivacaine	Number of patients
Levin *et al. (183)*	0	0	48
Hughes *et al. (184)*	8	1*	40
Lim *et al. (185)*	5	2*	40
Camorcia *et al. (186)*	8	1	64
TOTAL	21	4	192

For levobupivacaine less information is available. Lacassie et al. determined the motor block MLAC concentration of levobupivacaine and bupivacaine using a model of up-and-down sequential allocation *(187)*. These authors noted that levobupivacaine was significantly less potent for motor block then bupivacaine, at 87% that of bupivacaine. Vercauteren *et al*. observed no clinical differences between spinal levobupivacaine and racemic bupivacaine except for less motor block with levobupivacaine *(188)*.

The clinical relevance of reduced potency

So-called MLAC studies have repetitively demonstrated that ropivacaine and levobupivacaine are less potent during labour analgesia at the ED50 point of the dose-response curve then bupivacaine *(189–191)*. Although MLAC studies have undoubtedly added to our understanding of local anaesthetics and their relative potency, there are several caveats when applying these results to the clinical situation of labour analgesia. First, MLAC studies only focus on one point of the dose response curve and provide no information on the slopes of the different dose response curves. Second, MLAC studies only focus on the concentration used and not on the total dose. However total dose, determines the intensity of sensory and motor block *(192)*. Third, it is difficult to control for confounding factors such as stage of labour, parity, type of labour, etc…, factors that each individually impact on labour pain intensity. Fourth, MLAC studies determine relative potency for initiation of analgesia during labour, but do not provide information on relative potency during maintenance of analgesia (which might be influenced by factors such as local anaesthetic lipid solubility or effects of local anaesthetics on epidural vasculature). However, despite these criticism, most clinicians would agree that new local anaesthetics are indeed less potent then bupivacaine. Recently this has been confirmed by the first full dose response comparison of levobupivacaine, ropivacaine and bupivacaine, used for spinal labour analgesia *(193)*. Other authors did propose a potency hierarchy: bupivacaine > levobupivacaine > ropivacaine *(186)*.

Clinicians live, however, in the real world. Most of us are not interested in the ED50, but want all are patients to be without pain. This means we will overdose some patients, to achieve good analgesia for all. Various solutions to minimize overdosing have been successfully investigated such as patient controlled epidural analgesia (PCEA). It is this authors conviction that the new local anaesthetics contribute to minimizing the side-effects of systematic overdosing, which is unavoidable in many patients.

CONCLUSION

Ropivacaine and levobupivacaine are safer drugs, have less prolonged motor block following Caesarean section, demonstrate greater motor-sensory separation during labour analgesia, and result in better neonatal and labour outcome when higher concentrations of local anaesthetics are used throughout labour. Unfortunately until now no study could identify improved labor outcome with low concentrations of the new local anaesthetics. We feel that the slightly increased cost is justified by the advantages in terms of safety and motor block and we are convinced that every institution should replace bupivacaine by one of its newer alternatives, as have done we!

Adjuvant drugs

Different adjuvant drugs have been tested for use in neuraxial labour analgesia: opioids, clonidine, neostigmine, epinephrine, magnesium and adenosine.

Opioids

Opioids used for labour pain relief act through mechanisms in the dorsal horn. Activation of μ, δ and κ- receptors induces pre-synaptic inhibition of neurotransmitter release and produces post-synaptic neuronal membrane hyperpolarisation.

Pure epidural opioid analgesia is feasible in the early stages of labour. Capogna et al. determined the ED50 of epidural fentanyl and sufentanil using the MLAC methodology *(194)*. To produce analgesia in 50% of patients a dose of 124 μg fentanyl and 21 μg sufentanil was required, establishing a potency ratio of 5.9 between sufentanil and fentanyl.

However, usually opioids are combined with local anaesthetics. It has been repeatedly shown that opioids have a synergistic effect with various local anaesthetic agents. Opioids reduce the ED50 of different local anaesthetics *(195)*. In clinical practice the addition of opioids reduces the onset of analgesia, prolongs the duration of initial epidural analgesia, reduces local anaesthetic consumption and decreases the incidence of patients with insufficient analgesia *(196)*. The incidence of troublesome motor block is reduced and the rate of spontaneous vaginal delivery is increased *(196)*. Unfortunately, more patients experience pruritus *(196)*.

Plain intrathecal opioids are successful in producing labour analgesia. Palmer et al. established that fentanyl

25 μg was the optimal intrathecal dose *(197)*. 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 *(198)*. However, certainly in Europe, most anaesthesiologist prefer the intrathecal combination of local anaesthetics and opioids. Adding opioids to the spinal mixture, reduces the ED50 of the local anaesthetic agent and prolongs dose-dependently the duration of initial spinal analgesia *(199)*.

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 *(27)*. Usually these changes were related to uterine hyperactivity and not maternal hypotension *(27)*. Several authors postulated that an imbalance between maternal cathecholamines following rapid spinal analgesia produces uterine hypertonicity *(27)*. 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 *(27)*.

Clonidine

Clonidine, an α_2-receptor agonist, acts through α_2-receptors located in the dorsal horn to produce labour analgesia. Pre-synaptic stimulation of α_2-receptors inhibits neurotransmitter release and post-synaptic stimulation prevents neuronal transmission through hyperpolarisation. Animal safety studies established that clonidine was not neurotoxic and did not affect spinal cord blood flow *(200, 201)*.

A limited number of clinical trials have studied various doses (30–150 μg) of epidural clonidine during labour. Based on the MLAC methodology, a minimum of 60 μg clonidine is required to reduce the ED50 of ropivacaine for labour analgesia *(202)*. Doses above 100 μg induce maternal hypotension, bradycardia and sedation and in some trials also new onset foetal heart rate changes *(203)*. Based on a dose response study of Brichant et al. and recent work by Landau *et al.* we conclude that the optimal epidural dose of clonidine is probably 75 μg *(204, 205)*. Prolonged analgesia, reduced local anaesthetic consumption, less epidural top-ups for breakthrough pain without an increase in side effects were noted *(204, 205)*.

Chiari *et al.* studied the use of pure spinal clonidine labour analgesia *(206)*. This seems not feasible since doses producing adequate analgesia also induce unacceptable side effects such hypotension. Adding lower doses of clonidine (15–45 μg) to spinal analgesics does improve the duration and quality of initial spinal analgesia *(207, 208, 209)*. However, especially when clonidine is combined with local anaesthetic agents, significant and prolonged hypotension is likely to occur *(208, 209)*.

Epinephrine

Epinephrine also acts through α_2-receptors. However vascular effects, especially with epidural administration might also be involved.

Epidurally administered epinephrine significantly reduces the MLAC concentration of bupivacaine in labouring patients and improves the quality of analgesia *(210)*. 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 *(211)*.

Unfortunately, epinephrine also induces an increased incidence of maternal motor deficit especially when administered epidurally or intrathecally *(212, 213)*. Minute doses (2.25 μg) of spinal epinephrine were not associated with more motor block. Epidural epinephrine might also prolong labour duration by ß-agonist effects, especially when higher doses are infused in the epidural space *(212–216)*. Furthermore adding epinephrine to pharmacist pre-prepared solutions complicates storage and significantly increases the price of handling and preparation. Thus, this author has abandoned the addition of epinephrine from the local anaesthetic solution used for spinal and epidural administration.

Neostigmine

Acetylcholine is an important neurotransmitter in the dorsal horn of the spinal cord for the descending inhibitory pathways. Neostigmine, a cholinesterase inhibitor, increases the concentration of acetylcholine in the synapses and thus stimulates analgesia by stimulating acetylcholine mediated mechanisms of analgesia. Naguib and Yaksh demonstrated that the analgesic effects of neostigmine and clonidine are synergistic *(217)*. Following reassuring safety studies, in which no neurotoxic effects and no detrimental effects on spinal cord perfusion were identified, neostigmine has been evaluated for labour pain relief *(218, 219)*.

Several trials evaluated the effects of epidural neostigmine *(220, 221)*. Neostigmine seems to be promising as an adjuvant drug for labour analgesia.

Nelson et al. investigated the analgesic potential and side effect profile of 5, 10, 20 μg intrathecal neostigmine alone *(222)*. From this first phase, 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 duration of analgesia of neostigmine was observed. D'Angelo *et al.* however reported no increase in analgesic duration with neostigmine as part of a multi-drug combination (local anaesthetic, opioid, clonidine and neostigmine) *(223)*. Furthermore several authors reported a very high incidence of severe nausea and vomiting *(224)*.

Other drugs: magnesium and adenosine

Both adenosine and magnesium have been added to intrathecal opioids to relief labour pain *(224, 225)*. No significant advantages of adding adenosine to the analgesic mixture were observed. Magnesium prolonged intrathecal fentanyl analgesia.

Conclusion

Local anaesthetic agents combined with opioids remain the cornerstone of effective spinal and epidural labour analgesia. Epidural clonidine is a valuable adjuvant drug, especially in difficult to control labour pain. An epidural dose of 75 μg seems safe and effective. Spinal clonidine is effective but has been shown to induce difficult to control hypotension and should therefore be reserved for very specific situations. Routine us cannot be recommended by this author.

Epinephrine is a valuable drug but potential problems such as motor block, detrimental effects on the progress of labour and storage problems limit its usefulness. With neostigmine limited clinical experience is available. Spinal neostigmine produces unacceptable nausea and vomiting. Adenosine and magnesium have recently been studied during labour analgesia. Preliminary data are disappointing.

CONCLUSIONS

Based on experience and review of the literature, this author would answer the initial questions as follows:

How should we initiate labour analgesia?: Use a CSE because it provides reliable, fast analgesia with low doses of analgesic drugs and improves the effectiveness of your epidural catheter.

How should we maintain analgesia?: PCEA is the way forward.

Which local anaesthetic should we use? Probably, but still controversial, either ropivacaine or levobupivacaine because the possibility of less motor block.

Which adjuvant drugs?: Opioids, both epidurally and intrathecally, certainly whilst epidural clonidine and neostigmine are good candidates which need further study.

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