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REVIEW ARTICLE

Update on modern neuraxial analgesia in labour: a review of the literature of the last 5 years

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Summary

Several strategies and alternative therapies have been used to provide analgesia for labour pain. Over the last few years, a number of improvements have enhanced the efficacy and safety of neuraxial analgesia and ultimately have improved mothers' satisfaction with their birth experience. As labour analgesia is a field of obstetric anaesthesia that is rapidly evolving, this review is an update, from a clinical point of view, of developments over the last 5–7 years. We discuss advantages and controversies related to combined spinal-epidural analgesia, patient controlled epidural analgesia and the integration of computer systems into analgesic modalities. We also review the recent literature on future clinical and research perspectives including ultrasound guided neuraxial block placement, epidural adjuvants and pharmacogenetics. We finally look at the latest work with regards to epidural analgesia and breastfeeding.

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Several strategies and alternative therapies have been used to provide analgesia for one of women's most painful experiences in life, labour pain. These include non-pharmacological approaches such as hypnosis, acupuncture, hydrotherapy and transcutaneous electrical nerve stimulation as well as the administration of nitrous oxide and low-dose sevoflurane and parenteral opioids. Although some of these therapies provide satisfactory pain relief from the mothers' point of view [1, 2], there is evidence that neuraxial local anaesthetics and opioids yield superior and more reliable analgesia than these aforementioned methods [3, 4].

Although invasive, neuraxial labour analgesia is considered safe practice. Over the last decade, several improvements have enhanced the efficacy and safety of neuraxial analgesia and ultimately have improved mothers' satisfaction with their birth experience. These developments include the introduction of combined spinal-epidural (CSE) analgesia, 'mobile epidurals', patient controlled epidural analgesia (PCEA), computer assisted injection of epidural solutions and ultrasound guided neuraxial techniques. Some of these advances have already been introduced into clinical practice while ongoing research is stimulated by the exciting clinical perspectives brought forward by other developments. This review focuses on the recent advances in neuraxial labour analgesia and on the relevant scientific literature published in the last 5 years. We performed a MEDLINE-based search of all the literature published from January 2005, using the following keywords: labour analgesia; epidural; spinal; combined spinal-epidural; pregnancy; obstetric; neostigmine; clonidine; pharmacogenetics; and breastfeeding. We focussed our research on prospective, randomised controlled trials as well as meta-analysis and further completed our review by including retrospective observational trials and case reports where relevant. For clarity of discussion and when considered necessary, we also included literature from earlier years.

Initiating neuraxial analgesia

Ultrasound guided neuraxial techniques

Ultrasound imaging is becoming an increasingly popular aid for performing neuraxial blockade. It may help to identify the midline, localise the epidural space,

measure the skin-to-epidural space distance and estimate the angle of needle insertion [5]. It is suggested that prepuncture lumbar ultrasound assessment provides the clinician with useful anatomical information, which may facilitate the placement of epidural needles not only in healthy parturients but also in obese pregnant women and patients with scoliosis [5–8]. It also has been shown that ultrasonography, used as a teaching tool, improves the epidural placement learning curve by increasing epidural success rate and reducing the number of epidural attempts and catheter replacement for failed labour analgesia [9, 10]. Finally, ultrasound technology opens the door to new research perspectives such as a better understanding of the physiology and pharmacology of neuraxial blockade and the development of a 'difficult spine score' similar to scores developed to predict difficult airway management [5]. A description of the technical aspects and a review of the considerations pertaining to ultrasonography for lumbar epidural anaesthetic procedures is beyond the scope of this article and we invite the reader to consult an excellent review by Carvalho on the subject [5].

Combined spinal-epidural analgesia

Combined spinal-epidural analgesia has become a widely popular alternative to low-dose epidural analgesia for labour [11]. As its name implies, the CSE technique consists of a spinal injection of a small dose of local anaesthetic and/or lipophilic opioid (usually fentanyl or sufentanil), followed by the introduction of a catheter into the epidural space, for maintenance of analgesia. This protocol potentially provides the advantages of a spinal anaesthetic with a fast onset of analgesic action, reliable anaesthesia of sacral roots, a high quality of analgesia especially during the second stage of labour, high maternal satisfaction and low maternal and cord blood drug concentrations. It also allows the anaesthetist to supplement and titrate analgesia using the indwelling epidural catheter [12–14]. Several prospective trials [15–20] and a recent meta-analysis [21] reviewing over 2500 women in 19 randomised controlled trials have consistently demonstrated a faster onset of analgesia (of approximately 10 min [13]) with a CSE than with a standard low-dose epidural technique, while both approaches provide high quality analgesia and excellent maternal satisfaction. Owing to the subarachnoid injection of opioids, CSE analgesia has been associated with a greater incidence of pruritus than epidural analgesia [20–22].

Despite the increasingly widespread use of this technique and the numerous published investigations, the optimal intrathecal drug regimen has not yet been determined. Moreover, these studies have examined potential CSE-associated adverse events such as fetal heart rate abnormalities, post-dural puncture headache and lower limb motor block, which are addressed in this review.

Local anaesthetic dose for CSE

With the aim of determining the optimal intrathecal regimen that would provide the most efficacious labour analgesic while minimising adverse effects, several combinations of spinal local anaesthetics with lipophilic opioids have been studied [21] (Tables 1 and 2). The up-down sequential allocation method allows determination of the minimum (median) local anaesthetic dose (MLAD) for neuraxial analgesia and anaesthesia. The MLAD, which is an estimation of the median effective dose (ED_{50}) of a drug, is a research tool, from which the relative analgesic potencies of different local anaesthetic can then be obtained [23, 24]. Stocks et al. determined the MLAD for intrathecal bupivacaine without fentanyl and with fentanyl doses ranging from 5 to 25 μg [22]. The addition of fentanyl resulted in a dose-independent reduction of bupivacaine MLAD and a dose-dependant prolongation of analgesic effect but caused an increase in the incidence of pruritus. Camorcia et al. reported a greater analgesic potency for bupivacaine than for levobupivacaine and ropivacaine [25]. Sia et al. found a comparable ropivacaine: bupivacaine intrathecal potency ratio to that obtained by Camorcia et al. but the median effective doses (ED_{50}) determined by Sia et al. for levobupivacaine and ropivacaine were considerably smaller than those obtained by Camorcia et al. [26]. This observation, as well as the great variation in ED_{50} reported in Table 1, may be explained by several factors including differences in trial design in the definition of successful analgesia and the populations studied [27]. Interestingly, Parpaglioni et al. observed that the MLAD of levobupivacaine decreased as the intrathecal injection volume increased and showed that a 1-ml increase in the local anaesthetic volume almost doubled the effective response (odds ratio = 1.8) [28]. Patients receiving higher injectate volumes also demonstrated less hypotension and motor block. These results are in contrast to spinal anaesthesia for caesarean section, which is dependant upon the total local anaesthetic dose administered rather than on the subarachnoid injectate volume.

Table 1 Trials determining the median local anaesthetic dose for spinal local anaesthetic administered as part of a combined spinal epidural approach for labour analgesia.

Reference	n	Groups; drugs	MLAD; mg	Definition of efficacy	Comments
Stocks et al. [22]	120	n = 30; B n = 30; B+F 5 μg n = 30; B+F 15 μg n = 30; B+F 25 μg	1.99 (95% CI 1.71–2.27) 0.69 (95% CI 0.35–1.02) 0.71 (95% CI 0.00–1.53) 0.85 (95% CI 0.58–1.13)	VAPS ≤ 10 at 15 min PI	Baseline VAPS higher in group B+F 5 μg (86 mm) vs B+F 25 μg (68 mm) Speed of onset not affected by fentanyl Dose-dependant prolongation of analgesia and incidence of pruritus
Carmocia et al. [25]	89	n = 32; R n = 33; L n = 32; B	3.64 (95% CI 3.33–3.96) 2.94 (95% CI 2.73–3.16) 2.37 (95% CI 2.17–2.58)	VAPS ≤ 10 at 30 min PI	Analgesic potency ratio* at MLAD: B:L = 0.81 (95% CI 0.69–0.94) B:R = 0.65 (95% CI 0.56–0.76) L:R = 0.80 (95% CI 0.70–0.92) More motor impairment in patients receiving B and L than R
Parpaglioni et al. [31]	70	n = 35; L, spontaneous labour n = 35; L, induced labour	1.34 (95% CI 1.24–1.44) 1.95 (95% CI 1.84–2.06)	VAPS ≤ 10 at 20 min PI	Data expressed as MLAC in 10 ml: for spontaneous labour, MLAC was 0.0134% and for induced labour, MLAC was 0.0195% Patients with induced labour required analgesia earlier
Parpaglioni et al. [28]	90	n = 30; L in 10 ml n = 30; L in 5 ml n = 30; L in 2.5 ml	1.35 (95% CI 1.25–1.45) 1.63 (95% CI 1.51–1.76) 1.97 (95% CI 1.89–2.05)	VAPS ≤ 10 at 15 min PI	Duration of effective analgesia longer with smaller volume: mean (SD) 66.8 (15.6) min vs 91.1 (12.4) min for groups 10 and 2.5 ml, respectively Incidence of light motor block (Bromage score = 1) of 53.5% in group 2.5 vs 0% in groups 5 and 10 Incidence of maternal hypotension of 46.7% in group 2.5 vs 0% in groups 5 and 10
Sia et al. [26]	100	n = 50; L n = 50; R	1.07 (95% CI 0.88–1.25) 1.40 (95% CI 1.20–1.61)	VAPS < 10 at 15 min PI	The MLAD was derived from probit analysis after the patients were randomly allocated to receive 1 of 5 doses (1, 1.5, 2, 2.5, or 3 mg) of the respective LA Analgesic potency ratio at MLAD: L:R = 0.76 (95% CI 0.50–0.96)
Van de Velde et al. [27]	433	n = 145; B+S 1.5 μg n = 142; R+S 1.5 μg n = 146; L+S 1.5 μg	1.7 (95% CI 1.4–1.9) 2.2 (95% CI 1.8–2.6) 2.3 (95% CI 2.0–2.7)	VAPS < 25 at 15 min PI and for 45 min PI	The MLAD was derived from probit regression after the patients were randomly allocated to receive 1 out of 6 doses (1, 1.5, 2, 2.5, 3 or 3.5 mg) of the respective LA Analgesic potency ratio at MLAD: B:L = 0.7 (95% CI NA) B:R = 0.8 (95% CI NA) L:R = 1.0 (95% CI NA)

B, bupivacaine; F, fentanyl; VAPS, visual analogue pain score; PI, postspinal injection; R, ropivacaine; L, levobupivacaine; MLAD, minimum local anaesthetic dose; MLAC, minimum local anaesthetic concentration; LA, local anaesthetic; NA, not available.
*The analgesic potency ratio is determined by dividing the MLAD of one local anaesthetic by the other. The smaller the ratio, the greater the analgesic potency of the first local anaesthetic compared to the second. A ratio of 1 indicates equal potencies.

Table 2 Trials determining the ED_{95} for spinal local anaesthetics administered as part of a CSE regimen for labour analgesia.

Reference	n	Groups; drugs	ED_{95} (mg)	Definition of efficacy	Comments
Sia et al. [26]	100	n = 50; L n = 50; R	1.61 (95% CI 1.37–2.14) 2.12 (95% CI 1.81–2.81)	VAPS ≤ 10 at 10 min PI	No block failure in patient who received 2.5 mg or more of both LA
Whitty et al. [30]	40	n = 40; B+F 15 μg	1.66 (95% CI 1.50–482.5)	VAPS ≤ 10 at 10 min PI	100% success with 1.75 mg No motor block
Van de Velde et al. [27]	433	n = 145; B+S 1.5 μg n = 142; R+S 1.5 μg n = 146; L+S 1.5 μg	3.3 (95% CI 2.9–4.1) 4.8 (95% CI 4.0–6.7) 5.0 (95% CI 4.1–7.0)	VAPS < 25 at 15 min PI and for 45 min PI	The ED_{95} was extrapolated from probit regression after the patients were randomly allocated to receive 1 outs of 6 doses (1, 1.5, 2, 2.5, 3 or 3.5 mg) of the respective LA Analgesic potency ratio* at ED_{95}: L:R = 1.0 (95% CI 0.7–1.4) B:R = 0.71 (95% CI NA) B:L = 0.67 (95% CI NA) Duration of analgesia determined by the dose used, not the drug Onset of analgesia faster with B than with R and L
Parpaglioni et al. [31]	70	n = 35; L, spontaneous labour n = 35; L, induced labour	1.56 (95% CI 1.31–1.81) 2.27 (95% CI 1.94–2.66)	VAPS ≤ 10 at 20 min PI	Data expressed as ED_{95} in 10 ml: for spontaneous labour, MLAC was 0.0156% and for induced labour, MLAC was 0.0227% ED_{95} extrapolated from MLAC? Statistical methodology not clear

ED95, effective dose in 95% of the population; L, levobupivacaine; R, ropivacaine; VAPS, visual analogue pain score; PI, postspinal injection; LA, local anaesthetic; B, bupivacaine; F, fentanyl; S, sufentanil; NA, not available; MLAC, minimum local anaesthetic concentration.
*The analgesic potency ratio is determined by dividing the minimum local anaesthetic dose of one local anaesthetic by the other. The smaller the ratio, the greater the analgesic potency of the first local anaesthetic compared to the second. A ratio of 1 indicates equal potencies.

Although a useful research tool, the information provided by MLAD studies is not suitable for the clinical setting [23]. A common regimen for the spinal bolus of a labour CSE analgesia, which was reported in six trials reviewed by Simmons et al. [21] and used in other prospective trials [16, 29], consists of bupivacaine 2.5 mg with fentanyl 25 μg. The effective dose in 95% of the population (ED_{95}) is a more valuable approximation of a clinical dose and can be estimated from an up-down sequential allocation model, albeit with some degree of error [30]. Sia et al. determined the ED_{95} for levobupivacaine and ropivacaine without opioids and showed that at a dose of 2.5–3 mg, both local anaesthetics provided efficacious analgesia in all patients [26]. Whitty et al. determined that the ED_{95} of intrathecal bupivacaine with fentanyl 15 μg was 1.66 mg (95% CI 1.50–482.5 mg). The high upper range of 95% CI was acknowledged by the authors as a statistical anomaly but concluded that the success rate of sensory block was 100% in patients who received 1.75 mg [30]. Van de Velde et al. determined the full-dose response for racemic bupivacaine and the *S*-enantiomer of levobupivacaine and ropivacaine, all with sufentanil 1.5 μg [27]. The authors showed that bupivacaine was more potent than both ropivacaine and levobupivacaine but the values of ED_{95} obtained were considerably higher than those obtained by Sia et al. and Whitty et al. [26, 30]. Finally, Parpaglioni et al. demonstrated that when labour is induced, the ED_{95} (and the MLAC) for levobupivacaine was significantly higher than that when the labour is spontaneous [31]. With the exception of the study by Van de Velde et al., the findings from the other trials presented in Table 2 and from Lim et al. suggest that at a dose of 2.5 mg intrathecally, all local anaesthetics clinically used for CSE labour analgesia, with or without lipophylic opioids, should provide adequate analgesia [32].

'Dural puncture epidural' technique

Early in vitro and non-obstetric studies suggest a possible transfer of epidurally injected solutions into the cerebrospinal fluid (CSF) through the dural hole

created during the CSE technique with an improvement in epidural analgesia quality [33, 34]. The benefit of the 'dural puncture epidural' technique – whereby a dural hole is made with a spinal needle but the anaesthetic solution is injected only in the epidural space and not in the CSF – has been recently investigated during labour. Thomas et al. randomly allocated 251 parturients requiring neuraxial labour analgesia to receive a traditional epidural technique or a dural puncture epidural with a 27-G spinal needle [19]. After receiving an initial incremental epidural bolus of 10 ml lidocaine 2%, all patients were given PCEA. The sensory block height, incidence of unilateral sensory block, number of top-ups and PCEA volume used were similar between the groups. In a similar trial design, Cappiello et al. randomly allocated 80 parturients in labour into two groups: traditional epidural technique vs a dural puncture epidural technique with a 25-G spinal needle [35]. Following an initial epidural bolus of 12 ml bupivacaine 0.25%, PCEA was initiated. The investigators found that the dural puncture, without subarachnoid drug injection, resulted in more women with a visual analogue pain score < 10/100 at 20 min postinjection of the epidural solution, a reduced incidence of unilateral block, and an increased likelihood of achieving a sensory block to S1. Although these results suggest a translocation of local anaesthetic through the duralhole when the dural puncture is performed with a 25-G but not 27-G spinal needle, firm conclusions cannot be drawn because of the variability in the local anaesthetic used, the drug concentration and the bolus size. Further research is warranted to investigate the benefit and safety of dural puncture without spinal drug injection.

Motor block and maternal hypotension

As investigators do not address neuraxial analgesia adverse effects as primary endpoints, trials may be underpowered to detect statistically significant differences with regards to the incidence of motor block and maternal hypotension. The heterogeneity in CSE and epidural analgesia regimens, and the limited knowledge with regards to the sensory block equipotency of epidural and intrathecal local anaesthetic, may explain conflicting results. For example, Nakamura et al. observed that patients who received a CSE experienced significantly greater motor blockade than those who received epidural analgesia, whereas Van de Velde et al. reported the opposite results [36, 37]. Lim et al. showed that intrathecal bupivacaine 2.5 mg causes greater motor blockade than equal doses of ropivacaine and levobupivacaine (number of patients unable to raise extended legs but able to move knees and ankles was 5/20 for bupivacaine, 2/20 for ropivacaine and 0/20 for levobupivacaine) [32]. At sensory equipotent doses, Camorcia et al. observed significantly more motor blockade with bupivacaine and levobupivacaine than with ropivacaine [25]. However, in this MLAD study, none of the patients who received less than 2.25, 3.25 and 3.75 mg of the respective local anaesthetics presented any degree of lower limb motor blockade. At a dose of bupivacaine 1.75 mg or less, with fentanyl 15 μg, no patient evaluated by Whitty et al. presented with motor blockade [30]. These results suggest that when intrathecally administered, bupivacaine may have greater motor blockade potency than levobupivacaine and ropivacaine; but at clinical doses for labour analgesia, the incidence of motor block is low and should not be of concern to the clinician.

The same observations pertaining to the incidence of motor block can apply to maternal hypotension. While some studies show more maternal hypotension with CSE analgesia [16, 37, 38], others fail to show a significant difference [22, 25, 26]. It is noteworthy that in all trials reviewed, each episode of hypotension was easily treated with an intravenous fluid bolus and/or low-dose vasopressors and did not cause any maternal or neonatal morbidity.

Simmons et al. evaluated these endpoints in their recent meta-analysis and concluded that overall, the relative risk of these adverse outcomes was not increased by any of the anaesthetic techniques [21]. The clinician's decision to perform either one or the other analgesic technique should, therefore, not be primarily based on these possible side-effects.

Post-dural puncture headache

The possibility that the dural hole performed during a CSE may increase the incidence of post-dural puncture headache in comparison to a traditional epidural technique has been investigated in several retrospective and prospective trials [38–42]. All trials reported a similar low incidence (approximately 1%) of headache, regardless of the neuraxial analgesia procedure performed, findings that were confirmed by Simmons et al. [21]. As this adverse event is rare, these studies may be underpowered to detect a statistical difference between the anaesthetic techniques. Indeed, Norris et al. indicated that: 'a study with an 80% chance of

detecting an increase in positional headache from 1.6% to 2.1% would require more than 10 000 patients per group' [41]. As the incidence of post-dural puncture headache following CSE analgesia when using 25- to 27-G pencil-point spinal needles is low, we suggest that the clinicians should not primarily base their decision to perform a CSE on the risk of post-dural puncture headache.

Fetal heart rate abnormalities

Several investigators have described episodes of fetal heart rate (FHR) abnormalities following the spinal injection of analgesic solutions. Recently, Abrão et al. measured the incidence of uterine hypertonus and FHR abnormalities in a population of women in labour, randomly allocated to receive either CSE analgesia or epidural labour analgesia [43]. The investigators showed that the use of CSE analgesia was an independent predictor of uterine hypertonus (CSE: epidural OR 3.53; (95% CI 1.21–10.36)) and that the only predictor of FHR abnormalities was an increase of 10 mmHg or more in baseline uterine tone (OR 18.62; 95% CI 4.46–77.72). The authors also demonstrated that a decrease in visual analogue pain scores independently predicted a simultaneous occurrence of FHR abnormalities and uterine hypertony (OR 0.772; 95% CI 0.598–0.998). The FHR and tone changes were monitored only for 15 min following the performance of the analgesic procedure and the visual analogue pain scores were lower in patients receiving the CSE (not surprisingly, as the onset of analgesia is slower with epidurals). Therefore, experts suggested that the findings of this study might be ascribed to a difference in the intensity of analgesia rather than to the techniques per se [44]. Moreover, these authors pointed out that similar FHR and uterine tone changes might have occurred after the 15-min study period in the epidural group.

In a meta-analysis reviewing 24 trials (3513 women) of randomly allocated comparisons of intrathecal opioid with any analgesic regimens excluding spinal opioids in labour, Mardisoroff et al. found that the odds ratio for fetal bradycardia was significantly increased in patients who received subarachnoid opioids (OR 1.81 (95% CI 1.04–3.14)) and that for every 28 women receiving intrathecal opioids, one fetus would show bradycardia within the hour following administration of the drug [45]. The pathophysiological explanation for this phenomenon has been ascribed to the spinal block-induced rapid onset of analgesia, which results in a sudden drop in plasma adrenaline and β-endorphins but not of noradrenaline and oxytocin [46, 47]. In vitro findings suggest that this imbalance in plasma catecholamine would lead to uterine hypertonus and reduced blood flow [48]. This explanation has, however, been questioned by Van de Velde et al. who showed in a randomly allocated trial that the onset of labour analgesia was as rapid and of similar magnitude in patients receiving spinal bupivacaine 2.5 mg with sufentanil 1.5 μg and adrenaline 2.5 μg, compared with patients receiving only spinal sufentanil 7.5 μg [37]. The authors observed an incidence of non-reassuring fetal heart rate patterns of 24% in the sufentanil-only group and 12% in the bupivacaine/sufentanil/adrenaline group, a difference that was not explained by maternal hypotension. They also showed an incidence of uterine hyperactivity of 12% vs 2% for the sufentanil-only and bupivacaine/sufentanil/adrenaline groups, respectively. These results suggest that other factors (other than the sudden drop in pain level, the imbalance in plasma catecholamines and the consequential uterine hyperactivity) associated with intrathecal opioids may play a role in the development of FHR abnormalities. The clinical relevance of these abnormal FHR recordings is controversial. Mardirosoff et al. could not demonstrate any significant clinical effect of intrathecal opioids on 5-min Apgar scores or on instrumental delivery and caesarean rates whereas Van de Velde et al. reported that none of the non-reassuring FHR patterns in their trial resulted in serious maternal or neonatal morbidity [37, 45]. However, Clarke et al. and Cortes et al. both reported two women requiring emergency caesarean section for persistent fetal bradycardia, which was associated with uterine hypertonus but not with maternal hypotension [15, 49]. All patients described by these investigators had received intrathecal fentanyl for labour analgesia. In one of these two women reported by Clarke et al., the 1-min Apgar score was 3 although all newborns reported in that series presented a 5-min Apgar score of 7 or more.

In a letter to the editor, Van de Velde stated that the association between subarachnoid opioids and transient fetal bradycardia was a real problem and queried whether we should avoid using spinal opioids in cases when fetal distress or uterine hypertony is present before induction of labour analgesia [50]. We also agree that the indication for the use of spinal opioids for labour analgesia in this context (and maybe for all women) should be revisited as: (i) spinal bupivacaine

2.5 mg alone provides acceptable labour analgesia within 5 min and for more than 30 min [32, 51]; (ii) at this dose, spinal bupivacaine does not cause significant motor blockade, maternal hypotension and fetal bradycardia; and (iii) initiating an epidural infusion that contains opioids within 30 min following spinal injection, in comparison to 60 min or more, has been shown to reduce the incidence of breakthrough pain and to be safe [29]. Taking this inference into consideration, perhaps a CSE with subarachnoid injection of local anaesthetic without opioids followed by early initiation of epidural analgesia could provide satisfactory pain relief while minimising the risks of opioid-induced transient fetal bradycardia. Further research to explore this question is needed.

In summary, there is no strong evidence to support the routine use of one technique over the other for the initiation of neuraxial labour analgesia. As the CSE provides faster onset of analgesia and may more reliably anaesthetise the sacral nerve roots, its use in advanced labour or in the second stage of labour may result in a better quality of analgesia. However, the clinician must balance these advantages against the increased risks of FHR abnormalities associated with the subarachnoid injection of opioids. As noted by Preston, the decision to initiate neuraxial analgesia with a CSE or an epidural must be based on the mother's needs, the safety of the mother and the baby and the expertise within a given unit [13].

Continuous spinal analgesia

Continuous spinal analgesia consists of intentionally inserting a catheter through the dura into the intrathecal space and infusing or injecting successive boluses of local anaesthetic and/or opioids directly into the CSF. It therefore potentially provides reliable spinal analgesia throughout labour. Eleven case reports (non-obstetric patients) of cauda equina syndrome following continuous spinal analgesia prompted the US Food and Drug Administration (FDA) to require the manufacturer to withdraw spinal catheters smaller than 24-G from the market in North America. It was never determined, however, whether these complications were caused by these microcatheters or rather as a result of the intrathecal pooling of high-concentration (5%) hyperbaric lidocaine used in almost all of these patients. An excellent recent review by Moore summarises the history, clinical applications, concerns with regards to neurotoxicity and other considerations related to the use of continuous spinal anaesthesia [52].

In 1996, the FDA authorised the investigational use of 28-G spinal microcatheters to assess their safety and efficacy in pregnant women in labour. In a multicentre, prospective, randomised controlled trial, 325 women at term gestation and in labour received a continuous intrathecal infusion of sufentanil with intermittent bupivacaine boluses through a 28-G microcatheter. These parturients were compared with 100 women receiving labour analgesia with a bupivacaine- and sufentanil-based epidural regimen [53]. Arkoosh et al. demonstrated that analgesia was superior and provided better maternal satisfaction in parturients receiving continuous spinal analgesia compared with epidural analgesia [53]. There was no report of neurological complications solely attributed to the use of the microcatheters. However, the investigators reported a higher failure rate in the spinal catheter group, that was largely attributed to catheter dislodgement. The authors also observed a trend towards more post-dural puncture headaches in parturients with continuous spinal analgesia. The authors concluded that: 'larger studies would also improve our understanding of the expected rate of postdural puncture headache, optimal analgesic regimens and patient populations who can benefit the most from this technique'. It does not appear that the FDA plans to allow the marketing of such microcatheters in the near future.

Continuous spinal analgesia with dedicated macro catheters (22- or 24-G spinal catheter over 27- or 29-G needle) is more commonly used in other countries [54, 55]. In the UK, continuous spinal analgesia is occasionally used during labour for highly selected cases, whereby the clinician will intentionally puncture the dura with an epidural needle and thread a standard epidural catheter in the intrathecal space.

Maintaining neuraxial analgesia

Patient controlled epidural analgesia

Over two decades ago, Gambling et al. introduced PCEA for labour into obstetric anaesthesia practice [56]. Compared to continuous epidural infusion, PCEA has been proven to increase maternal satisfaction, reduce physician workload by reducing breakthrough pain requiring intervention by the anaesthetist, reduce consumption of local anaesthetic and decrease motor block [57, 58]. These results may be explained by experiments on human cadavers,

which have shown that the high injection pressure generated to administer a bolus results in a more uniform spread of the solution within the epidural space [59]. Also, PCEA theoretically allows the patients to tailor their analgesic requirements to their level of pain, which may vary throughout labour and from one patient to another. Although the benefits of PCEA are well recognised, the optimal PCEA regimen, dose ranges and settings have not been determined. We recommend an excellent systematic review by Halpern and Carvalho examining these issues [60]. In this section, we will review the recent advances with regards to the addition of a background infusion to the PCEA, the lockout interval and bolus dose volume, computer integrated PCEA, intermittent automated mandatory boluses and programmed intermittent epidural bolus with PCEA. We will focus on the recent literature and future perspectives.

Background infusion

Background infusion vs demand-only PCEA

The addition of a local anaesthetic background infusion to a PCEA for labour was first investigated in 1992 by Paech [61] (Table 3). In this randomised study, the author could not demonstrate that the addition of a 4 $ml.h^{-1}$ background infusion conferred any advantage over a demand-only PCEA in terms of pain relief, supplementary boluses and maternal satisfaction. Several trials investigated different background infusion rates (2–10 $ml.h^{-1}$), local anaesthetics and drug concentrations on the efficacy of PCEA with conflicting results [62–72]. Boselli et al. observed that the addition of a background infusion did not reduce visual analogue pain scores nor requests for nurse-administered supplemental boluses, but higher infusion rates (6 and 9 $ml.h^{-1}$) led to an increase in overall ropivacaine consumption [62]. Similar results were reported by Thénoz et al. who studied the use of levobupivacaine 0.0625% with sufentanil 0.5 $\mu g.ml^{-1}$ in a comparable trial design [72]. Bremerich et al., in contrast, demonstrated that a PCEA combined with a 4 $ml.h^{-1}$ background infusion resulted in fewer episodes of visual analogue pain scores > 4/10 and in fewer boluses requested and delivered [68]. The reduced incidence of breakthrough pain requiring medical input, associated with a background infusion, was confirmed in three recent studies [63, 71, 72]. In all studies, the background infusion led to a reduction in physician-administered top-ups for breakthrough pain.

Background infusion rate and efficacy

Of seven studies investigating 'low-rate' background infusion ($\leq$ 4 $ml.h^{-1}$) [61, 62, 67–70, 72], two [67, 68] reported a reduction in the incidence of anaesthetists' interventions for treating breakthrough pain. In contrast, out of seven studies investigating 'high-rate' background infusion ($\geq$ 5 $ml.h^{-1}$) [62–66, 70, 72], four [63–65, 70] reported a reduced incidence of the same outcome. It does appear from this review that there might be a benefit of using a 'high-rate' over a 'low-rate' background infusion. A meta-analysis of these studies is needed to draw conclusions on the advantage of increasing background infusion rates in terms of pain scores, breakthrough pain, maternal satisfaction and physician interventions.

Background infusion rate and local anaesthetic consumption

There appears to be a relationship between the background infusion rate and local anaesthetic consumption. Indeed, of seven studies investigating background infusion rates of 4 $ml.h^{-1}$ or less [61, 62, 67–70, 72], none reported an increase in local anaesthetic consumption. In contrast, of seven studies where patients received a background infusion rate of 5–10 $ml.h^{-1}$ [62–66, 70, 72], five [62–64, 66, 72] showed a significantly greater local anaesthetic consumption than in patients receiving no background infusion or a background infusion rate of 3 $ml.h^{-1}$. Moreover, Srivastava et al. found a non-statistically significant trend towards more local anaesthetic consumption in the PCEA + background infusion (10 $ml.h^{-1}$) group [65]. The clinical relevance of these administered local anaesthetic volume differences seems to be minimal, as the hourly difference in local anaesthetic consumption presented in many of these trials was relatively small (ropivacaine 4.3 mg [63], ropivacaine 4 mg [62] and levobupivacaine 4.4 mg [72]) and, most importantly, did not result in any impact on lower limb motor block, local anaesthetic toxicity or difference in the incidence of adverse events.

In summary, although there is conflicting evidence to support the systematic use of a background infusion with PCEA, we agree with Halpern and Carvalho that a background infusion added to a PCEA may improve patient analgesia [60], as several studies have demon-

Table 3 Trials comparing the background infusion added to PCEA.

Reference	n	Infusion rates	Regimen	Main results	Authors' conclusion
Peach [61]	50	n = 25; 0 ml.h^{-1} n = 25; 4 ml.h^{-1}	B 0.125% F 3 μg.ml^{-1} PCEA: Bolus 4 ml, LO 15 min	Greater fentanyl usage in the PCEA+BI group Pain relief, supplementary bolus required, maternal satisfaction similar in the two groups	The addition of a BI to PCEA confers no benefit
Ferrante et al. [70]	60	n = 15; 0 ml.h^{-1} n = 15; 3 ml.h^{-1} n = 15; 6 ml.h^{-1} n = 15; CEI 12 ml.h^{-1}	B 0.125% F 2 μg.ml^{-1} PCEA: Bolus 3 ml, LO 10 min	PCEA with or without a BI provided a LA sparing effect in comparison to CEI. More physician-administered supplemental bolus in PCEA-alone and with BI of 3 ml.h^{-1}	The administration of a significant but modest (i.e. 33%) of the maximum hourly demand dose as a continuous BI is appropriate for PCEA during labour and delivery
Petry et al. [69]	74	n = 37; 0 ml.h^{-1} n = 37; 3 ml.h^{-1}	B 0.125% S 0.75 μg.ml^{-1} A 1:800 000 PCEA: Bolus 3 ml LO 12 min	No difference between the groups	
Boselli et al. [62]	133	n = 34; 0 ml.h^{-1} n = 34; 3 ml.h^{-1} n = 32; 6 ml.h^{-1} n = 33; 9 ml.h^{-1}	R 0.1% S 0.5 μg.ml^{-1} PCEA: Bolus 5 ml LO 5 min Max 22 ml.h^{-1} including infusion	No difference in VAPS, number of supplemental bolus, maternal satisfaction Greater overall drug consumption with a 6 and 9 ml.h^{-1} BI	BI results in greater LA consumption without improving analgesia and maternal satisfaction
Bremerich et al. [68]	66	n = 33; 0 ml.h^{-1} n = 33; 4 ml.h^{-1}	R 0.16% S 0.5 μg.ml^{-1} PCEA: Bolus 4 ml LO 20 min in group with BI, 15 min in groups without BI	More episodes of VAPS > 40 mm in demand-only PCEA group No difference in any other outcome	PCEA+BI was more effective than demand-only PCEA in treating labour pain without increasing consumption of LA
Missant et al. [67]	78	n = 38; 0 ml.h^{-1} n = 40; 2 ml.h^{-1}	R 0.15% S 0.75 μg.ml^{-1} PCEA: Bolus 4 ml LO 15 min	More anaesthetist interventions for breakthrough pain in demand-only PCEA group. Greater LA consumption in PCEA-only group when physician-administered boluses included No difference in any other outcome	PCEA with a background infusion provides effective analgesia with reduced anaesthetist workload and reduced local anaesthetic consumption
Vallejo et al. [66]	189	n = 63; 0 ml.h^{-1} n = 64; 5 ml.h^{-1} n = 62; CEI 10 ml.h^{-1}	R0.10% F 2 μg.ml^{-1} PCEA Bolus 5 ml LO 20 min in group with BI, 15 min in groups without BI	Total LA consumption lower in demand-only PCEA group compared to PCEA+BI and CEI groups No difference in any other outcome	Demand dose-only PCEA results in smaller total epidural dose compared with CEI and PCEA+BI without affecting labour duration, motor block, VAPS, maternal and neonatal outcomes and maternal satisfaction

Table 3 (*Continued*)

Reference	n	Infusion rates	Regimen	Main results	Authors' conclusion
Lim et al. [63]	300	n = 100; 0 ml.h^{-1} n = 100 5 ml.h^{-1} n = 100 10 ml.h^{-1}	R 0.1% F 2 μg.ml^{-1} PCEA Bolus 5 ml LO 15 min in PCEA- only group, 12 min in group 5 ml.h^{-1}; 10 min in groups 10 ml.h^{-1} All groups: max 20 ml.h^{-1}	More breakthrough pain and higher VAPS in demand-only PCEA group in comparison to the other groups Increased LA consumption in group with BI of 10 ml.h^{-1}	Neuraxial labour analgesia administered via demand-only PCEA without background infusion cannot be considered practical
Okutomi et al. [64]	66	n = 33; 0 ml.h^{-1} n = 33; 6 ml.h^{-1}	R 0.1% F 2 μg.ml^{-1} PCEA Bolus 5 ml LO 10 min	LA consumption and number of self-administered bolus greater in group PCEA + BI in second stage of labour only	The use of a BI decreases PCEA demand dosing, but not the total hourly amount of ropivacaine and fentanyl used
Srivastava et al. [65]	55	n = 30; 0 ml.h^{-1} n = 25; 10 ml.h^{-1}	B 0.125% F 2 μg.ml^{-1} PCEA Group with BI: Bolus 3 ml LO 10 min PCEA-only group: bolus 8 ml LO 20 min. Max 25 ml.h^{-1}	More rescue bolus for breakthrough pain in demand-only PCEA group	The addition of background infusion to PCEA resulted in more constant pain relief with fewer episodes of distressing pain demanding rescue boluses from anaesthetist
Thénoz et al. [72]	96	n = 24; 0 ml.h^{-1} n = 24; 3 ml.h^{-1} n = 24; 6 ml.h^{-1} n = 24; 9 ml.h^{-1}	L 0.0625% S 0.5 μg.ml^{-1} PCEA Bolus 5 ml LO 5 min. Max 22 ml.h^{-1}	Hourly LA consumption lower in groups 0 and 3 ml.h^{-1} No difference in any of the other outcomes	Labour PCEA without or with a low background infusion can be efficiently used
Campbell et al. [71]	211	n = 104; 0 ml.h^{-1} n = 107; 10 ml.h^{-1}	R 0.8% F 2 μg.ml^{-1} PCEA Bolus 5 ml LO 10 min	Mean VAPS higher at each cervical dilation and more anaesthetist-administered rescue boluses in PCEA-alone group	PCEA with a BI provides more effective labour analgesia

PCEA, patient controlled epidural analgesia; B, bupivacaine; F, fentanyl; LO, lockout interval; BI, background infusion; CEI, continuous epidural infusion; LA, local anaesthetics; S, sufentanil; A, adrenaline; R, ropivacaine; VAPS, visual analogue pain score; L, levobupivacaine.

strated a benefit towards reduced breakthrough pain and fewer physician interventions with the addition of a background infusion. The data suggest that there is some advantage in using high-rate (≥ 5 ml.h^{-1}) infusions in terms of PCEA efficiency. However, increasing background infusion rates may lead to greater local anaesthetic consumption. To find a balance between fewer physician interventions and reducing local anaesthetic use, Smiley and Stephenson have suggested a strategy that consists of administering about a third of the expected local anaesthetic hourly demand as a background infusion [73].

Ongoing developments

An alternative approach to determine the background, infusion rates has been proposed by a group from Singapore [74–76]. These investigators recently developed 'computer integrated' PCEA (CI-PCEA). This drug delivery system enables a PCEA pump, connected to a computer, to titrate the background infusion rate based on PCEA demands. Comparing CI-PCEA to

PCEA without a background infusion, Lim et al. observed similar local anaesthetic consumption, visual analogue pain scores and breakthrough pain (a non-statistically significant trend towards less breakthrough pain in the CI-PCEA group) but higher maternal satisfaction in the CI-PCEA group [74]. Sia et al. found that CI-PCEA, compared with a continuous epidural infusion, reduced the incidence of breakthrough pain without increasing the local anaesthetic consumption [75]. Finally, Sng et al. compared CI-PCEA with PCEA plus a background infusion and also showed a higher maternal satisfaction with the CI-PCEA whereas the local anaesthetic consumption, visual analogue pain scores and incidence of breakthrough pain were similar in the two groups [76]. Interestingly, in this latter study, the infusion rate in the CI-PCEA group was higher during the second stage of labour, compared with PCEA plus a background infusion group. This fact may support earlier findings from Capogna et al. who showed an increased epidural local anaesthetic requirement as labour progresses [77]. It follows from these studies that an adjustable background infusion appears to increase maternal satisfaction and may further reduce the incidence of breakthrough pain without increasing local anaesthetic consumption.

PCEA lockout interval and bolus volume

Similar to the use of a background infusion, the optimal PCEA lockout interval and bolus volume are subject to debate (Table 4). Six studies have investigated bolus volumes ranging from 2 to 20 ml with lockout intervals ranging from 5 to 30 min [78–83]. There is wide variety between trials with regards to the type and concentration of anaesthetic solutions studied as well as to the use of a background infusion. Regardless of the regimen investigated, the majority of studies reviewed in this article reported no difference in outcomes such as visual analogue pain scores, maternal satisfaction, motor block and physician intervention for rescue analgesia. Stratmann et al. demonstrated that a shorter lockout interval resulted in a better bolus delivered/bolus attempt ratio (an index of PCEA efficiency) but did not lead to improvement in any other outcome [83]. The authors stated that they have used a 5-min lockout interval in their practice on over 15 000 patients with no report of adverse events. Bernard et al. randomly allocated 220 parturients to receive PCEA with a low-volume/short-interval setting (4 ml, 8 min) or high-volume/long-interval setting (12 ml, 25 min) [79]. At 6-cm cervical dilation, visual analogue pain scores were lower and maternal satisfaction greater in the high-volume/long-interval group but at the expense of greater local anaesthetic consumption. Siddick-Sayyid et al. reported a non-statistically significant trend towards fewer rescue analgesia interventions in patients receiving PCEA set at a 9-ml bolus with a lockout interval of 18 min as opposed to smaller volumes with shorter lockout intervals [82].

In summary, there is no strong evidence to favour one regimen over another although there is suggestion that high-volume/long-lockout interval settings may provide better labour analgesia. It appears that all combinations are safe but larger studies are needed to evaluate the risks of adverse events such as motor blockade, local anaesthetic toxicity, prolonged duration of labour and incidence of instrumental delivery.

Continuous epidural infusion vs automated mandatory bolus

Findings from early studies in the non-obstetric population suggest that hourly equal doses of local anaesthetics administered as regular intermittent boluses, as opposed to an infusion, provide superior analgesia, higher sensory block level and fewer interventions for treatment of breakthrough pain [84, 85] (Table 5). Several recent labour analgesia studies have confirmed these previous results [86–91]. Chua et al. compared regular epidural automated mandatory boluses of 5 ml every hour with a continuous epidural infusion of 5 $ml.h^{-1}$ after a CSE for labour analgesia [86]. The authors found that the median sensory block height was higher and that serial visual analogue pain scores were lower in the automated mandatory boluses group. Fettes et al. found a higher incidence of unilateral sensory block in patients receiving a continuous epidural infusion as opposed to subjects in the regular automated mandatory boluses group [87]. The authors also demonstrated a reduction in the requirements for manual rescue for breakthrough pain and a local anaesthetic sparing effect in the automated mandatory boluses group, results that were confirmed in many other trials [88–91].

To investigate whether the combination of PCEA with background automated mandatory boluses would provide a local anaesthetic sparing effect while improving maternal analgesia and satisfaction in comparison

Table 4 Trials comparing different bolus and lockout intervals for PCEA.

Reference	n	Groups	Regimen	Main results	Authors' conclusion
Bernard et al. [79]	203	n = 100; 4 ml q 8 min n = 103; 12 ml q 25 min	B 0.125% A 1:800,000 S 0.625 μg.ml^{-1}	Pain lower at 6 cm cervical dilation and at delivery, mothers satisfaction higher in 12q25 group Greater LA and sufentanil consumption in the 12q25 group	PCEA setting of a 12-ml bolus dose and a 25-min lockout interval can improve analgesia and patient satisfaction during labour
Bernard et al. [78]	150	n = 25; 12 ml R 0.1% → 6 ml R 0.2%** n = 25; 12 ml R 0.1% → 12 ml R 0.1% n = 25; 16 ml R 0.1% → 8 ml R 0.2% n = 25; 16 ml R 0.1% → 16 ml R 0.1% n = 25; 20 ml R 0.1% → 10 ml R 0.2% n = 25; 20 ml R 0.1% → 20 ml R 0.1% Lock out interval of 25 min for all patients	Early labour (cervical dilation < 4 cm): all patient received R 0.1% F 0.5 μg.ml^{-1} Active labour (cervical dilation > 4 cm): half of the patients received R 0.2% F 1 μg.ml^{-1}	During late labour, Max VAPS lower in patients receiving 20 ml of dilute solution compared to 6 ml of concentrated solution, but not 10 ml of concentrated solution No other difference between groups	Effectiveness of PCEA is dependent on drug mass rather than the volume or concentration administered
Stratmann et al. [83]	60	n = 29; 5 ml q 5 min n = 31; 5 ml q 15 min	B 0.125% F 2 μg.ml^{-1} All patients had a BI of 6 ml.h^{-1} Hourly maximum dose: 26 ml	Bolus/attempt ratio higher in 5q5 group No other difference between groups	Either regimen can be used in obstetrics, although the 5-min interval might be more efficient
Carvalho et al. [80]	220	BI 10 ml.h^{-1}: n = 30; 6 ml q 8 min n = 30; 12 ml q 16 min BI 15 ml.h^{-1}: n = 30; 6 ml q 8 min n = 30; 12 ml q 16 min	B 0.0625% S 0.35 μg.ml^{-1}	Total LA consumption increased in patients with 15 ml.h^{-1} BI. More request to stop the epidural for perceived motor weakness in the last group No other difference in outcomes	All regimens provide excellent analgesia with minimal physician workload
Gambling et al. [81]	68	n = 14; 2 ml q 10 min n = 14; 3 ml q 15 min n = 13; 4 ml q 20 min n = 14; 6 ml q 30 min n = 13; CEI 8 ml.h^{-1}	B 0.125% E 1:400 000 F 2.5 μg.ml^{-1}	Higher LA consumption in the 8 ml.h^{-1} infusion group Sensory level higher in the 6q30 and 8 ml.h^{-1} groups	PCEA is a safe and effective alternative to CEI irrespective of the initial dose variables
Siddik-Sayyid et al. [82]	75	n = 25; 3 ml q 6 min n = 25; 6 ml q 12 min n = 25; 9 ml q 18 min	B 0.1% F 2 μg.ml^{-1} All patients received a BI of 6 ml.h^{-1}	No difference between groups Non-statistically significant trend towards a decreased need for rescue analgesia in the 9q18 group	The three modes of PCEA + BI were equally effective for labour analgesia

PCEA, patient-controlled epidural analgesia; q, lockout interval; B, bupivacaine; A, adrenaline; S, sufentanil; LA, local anaesthetics; R, ropivacaine; F, fentanyl; VAPS, visual analogue pain score; BI, background infusion; CEI, continuous epidural infusion.

with PCEA plus a background infusion, Wong et al. randomly allocated 158 parturients in labour to receive PCEA (bolus 5 ml; lockout 10 min; hourly maximum 15 ml) through one infusion pump in combination with either automated mandatory boluses (6 ml every 30 min) or a background infusion (12 ml.h^{-1})

Table 5 Trial comparing continuous infusion to automated regular mandatory boluses.

Reference	n	Groups	Regimen	Main findings	Authors' conclusion
Chua et al. [86]	42	n = 21; bolus 5 ml every h n = 21; CEI at 5 ml.h^{-1}	R 0.1% F 2 μg.ml^{-1}	Lower VAPS in the bolus group. Higher sensory block during the first 3 h in the bolus group	Continuous intermittent boluses appear to be a good alternative to CEI for the maintenance of labour epidural analgesia
Fettes et al. [87]	40	n = 20; bolus 10 ml every h n = 20; CEI 10 ml.h^{-1}	R 0.2% F 2 μg.ml^{-1}	Three times more rescue bolus in the CEI group to maintain pain relief in comparison to intermittent group. LA sparing effect in the intermittent group	AMB represents a more efficacious mode of analgesia.
Sia et al. [90]	42	n = 21; Bolus 5 ml every h n = 21; BI 5 ml.h^{-1}	R 0.1% F 2 μg.ml^{-1}. All patient had PCEA (bolus 5 ml, LO 10 min)	Reduction of hourly consumption of ropivacaine in the bolus group Fewer self-boluses in the bolus group No difference in VAPS, breakthrough pain or other outcomes	PCEA with AMB could be a useful mode of maintenance of epidural analgesia
Lim et al. [89]	60	n = 30; Bolus 5 ml every 30 min n = 30; CEI 10 ml.h^{-1}	L 0.1% F 2 μg.ml^{-1}	Lower incidence of breakthrough pain and fewer anaesthetic interventions in bolus group	Intermittent regular bolus administration of epidural LA decreases breakthrough pain and, in busy obstetric units, may also serve to decrease the anaesthetist's workload
Lim et al. [117]	50	n = 25; Bolus 2.5 ml every 15 min n = 25; CEI 10 ml.h^{-1}	R 0.1%, F 2 μg.ml^{-1}	No difference in breakthrough pain, LA consumption or any other outcome	Low-volume intermittent regular bolus administration of epidural LA does not improve analgesic efficacy
Leo et al. [88]	62	n = 31; Bolus 5 ml every h n = 31; BI 5 ml.h^{-1}	R 0.1% F 2 μg.ml^{-1} All patient had PCEA (bolus 5 ml, LO 10 min)	Less LA consumption and higher maternal satisfaction in the PCEA + AMB group	
Wong et al. [91]	126	n = 63; Bolus 6 ml every 30 min n = 63; BI 12 ml.h^{-1}	B 0.0625% F 2 μg.ml^{-1} All patient had PCEA (bolus 5 ml, LO 10 min)	Less hourly LA consumption, fewer manual rescue boluses and higher maternal satisfaction in the PCEA + AMB group	PCEA with AMB is superior to PCEA with BI for labour analgesia
Sa Peixoto et al. [118]	(48)*	(n = 24); Bolus 8 ml every h (n = 24); CEI 8 ml.h^{-1}	R 0.1% S0.25 μg.ml^{-1}	Fewer rescue boluses and decreased pain intensity with AMB bolus	Epidural analgesia by AMB is an effective technique

CEI, continuous epidural infusion; R, ropivacaine; F, fentanyl; VAPS, visual analogue pain score; LA, local anaesthetics; AMB, automated regular mandatory bolus; BI, background infusion; PCEA, patient-controlled epidural analgesia; LO, lockout interval; L, levobupivacaine; B, bupivacaine. *Data on number of patients analysed not available.

administered via a second infusion pump connected to the same epidural catheter [91]. The investigators confirmed their hypothesis by showing a local anaesthetic sparing effect and a reduction in the incidence of manual rescue boluses in the automated mandatory boluses group. One drawback of the independent two-pump setting used in this trial lies in the possibility that a mandatory bolus and a self-bolus may be administered

simultaneously and this could potentially result in an excessive amount of local anaesthetic injected in the epidural space.

Ongoing developments

To overcome this limitation, the group from Singapore designed a novel drug delivery system whereby a computer program enables an ordinary infusion pump to work as a PCEA pump with the ability to deliver automated mandatory boluses [88, 90]. The investigators also developed an algorithm that integrates the automated mandatory boluses with self-boluses such that the automated mandatory boluses may be delivered only after a predetermined PCEA lockout interval. The authors demonstrated that this 'programmed intermittent mandatory epidural bolus' with PCEA regimen provided advantages over a PCEA plus background infusion regimen in terms of local anaesthetic sparing effect, maternal satisfaction and duration of analgesia after the spinal component of a CSE in labouring parturients. They were, however, unable to show a difference in the incidence of breakthrough pain between the groups.

In summary, when compared to a continuous epidural infusion or a PCEA plus background infusion regimen, regular epidural automated mandatory boluses and PCEA plus automated mandatory boluses seem to reduce the consumption of local anaesthetic, while reducing the incidence of breakthrough pain requiring physician intervention. Several reasons may explain these findings. First, as mentioned earlier, the high driving pressure generated to inject a bolus may result in a more uniform spread of the solution in the epidural space [59]. Secondly, with the use of multi-orifice epidural catheters, solutions injected as a bolus exit the catheter through all the orifices and this results in a wider spread, as opposed to solutions injected as an infusion, which exit only through the proximal orifice [92]. Thirdly, many of the investigators studying automated mandatory boluses induced labour analgesia with a CSE (27-G pencil-point spinal needle) [86, 88–91]. It has been suggested that the high driving pressure associated with administering a bolus may cause some degree of direct transfer of the local anaesthetic solution into the intrathecal space through the dural hole [86]. However, Thomas et al. showed that a dural puncture with a 27-G needle did not improve epidural labour analgesia quality (vide supra) [19]. It is uncertain that there is a significant flux of local anaesthetic into the intrathecal space with repeated boluses in these patients, and more research is warranted to investigate the clinical benefit of intentional dural puncture in this context.

At the moment, several limitations preclude the routine use of a PCEA plus automated mandatory boluses regimen on labour wards. Firstly, there is no study comparing a PCEA plus automated mandatory boluses regimen with regular epidural automated mandatory boluses alone. Secondly, the two-pump setting used by Wong et al. is clinically cumbersome, may increase the risks of technical and drug delivery errors and is potentially expensive as twice the number of pumps would be needed [91]. Thirdly, although smart infusion pumps equipped with software allowing administration of epidural solutions within multiple infusion protocols are now marketed in the UK, programmes able to deliver local anaesthetic in a PCEA plus automated mandatory boluses mode are not yet available.

Adjuvants

The COMET group study has demonstrated that low-dose bupivacaine-based neuraxial analgesia for labour pain reduces the rate of instrumental vaginal delivery [93]. Such 'mobile' epidurals can give adequate labour analgesia provided the drug regimen includes adjuvants that will reduce pain transmission in an additive or synergistic fashion. Lipophilic opioids such as fentanyl and sufentanil have proven their efficacy and safety profile in millions of pregnant women. However, undesirable side-effects such as nausea, vomiting, pruritus and sedation led the medical community to search for alternative adjuvants, that might provide a local anaesthetic dose sparing-effect without producing unwanted side-effects. Epidurally administered clonidine (an α_2-receptor agonist, that modulates pain perception at spinal level) and neostigmine (an acetyl cholinesterase inhibitor, that indirectly stimulates both muscarinic and nicotinic receptors in the spinal cord) are promising agents and a few recent editorials have summarised the knowledge and future perspectives with regard to the use of these drugs for labour analgesia [94, 95].

The literature of the past 5 years has partially defined the dose, mode of administration and safety profile of both neostigmine and clonidine for labour analgesia. Two findings culminating from these studies are that (i) a combination of neostigmine and clonidine might provide superior labour analgesia while reducing

side-effects when compared with either one of these two drugs given alone and (ii) epidural infusion of clonidine may improve the side-effect profile of this agent as opposed to a bolus administration.

Roelants et al. compared a single epidural dose of clonidine (150 μg) with a single dose of neostigmine (750 μg) and with three combinations of clonidine (75 μg) and neostigmine (250, 500 and 750 μg) [96]. The authors observed that only the combinations of 75 μg clonidine with 500 or 750 μg neostigmine provided visual analogue scale pain scores significantly lower than baseline and that the effect was significantly longer than in the three other groups. Moreover, the combination of these two drugs did not result in any maternal adverse outcomes such as hypotension, nausea or sedation, or in any neonatal adverse outcome. Van de Velde et al. confirmed that a combination of clonidine 75 μg and neostigmine 500 μg administered epidurally as part of a CSE technique with ropivacaine and sufentanil did not result in maternal adverse effects [97]. Furthermore, the investigators were able to demonstrate that this combination prolonged the initial analgesic effect of the spinal component of the CSE and provided a subsequent local anaesthetic sparing effect.

Dewandre et al. determined that epidural clonidine 75 μg had the same local anaesthetic sparing effect as sufentanil 5 μg when administered as part of ropivacaine-based epidural analgesia [98]. However, the same group demonstrated that clonidine administered as a bolus resulted in greater maternal hypotension necessitating higher ephedrine and fluid requirements compared with an equipotent dose of sufentanil [99]. The authors concluded that based on these results, this dose of clonidine could not be recommended for labour epidural analgesia. Two groups have studied continuous epidural administration of clonidine for labour analgesia. Whether the epidural block was initiated with a low-dose clonidine bolus followed by continuous administration [100], or simply initiated as an infusion [101], this adjuvant resulted in lower pain scores and a local anaesthetic sparing effect. Although patients' sedation scores were not affected by the addition of clonidine, it resulted in statistically but not clinically significant decreases in maternal blood pressure. With regard to neostigmine, data from Ross et al. suggest that continuous epidural administration of this adjuvant also results in a bupivacaine sparing effect, even at doses (initial bolus of 60 μg followed by a potential maximal dose of 120 $\mu g.h^{-1}$) significantly lower than those described by Roelants et al. [96, 102].

Are we ready to use clonidine and neostigmine routinely as part of epidural labour analgesia regimens? The current evidence suggests that these agents might be added to the choices available for obstetric regional analgesia, providing obstetric anaesthetists with an alternative to epidural opioids if required. Many questions, however, remain unanswered. For instance, it is unclear whether clonidine or neostigmine should be administered as an initial bolus or as an infusion, whether they should be combined or administered separately, and what would be the optimal dose. Safety concerns have also been raised by some authors [94, 95]. In the scientific literature overall, fewer than a thousand parturients have been exposed to epidural neostigmine or clonidine in labour. Even fewer received these adjuvants as an infusion and no trial, to our knowledge, has investigated the infusion of clonidine and neostigmine in combination. Although no report of severe maternal or fetal adverse effect exists with the epidural delivery of these agents, we cannot draw the same conclusions as for opioids with regard to the safety and side-effect profile of these drugs in the context of epidural labour analgesia. Until these questions and issues are addressed in larger trials in the future, we do not recommend their routine use for labour epidural analgesia.

Pharmacogenetics

Clinicians are consistently confronted with variability in patients' sensitivity to pain stimuli and their response to analgesic drugs. Nociception is a complex phenomenon, undoubtedly influenced by a multitude of physiological, psychological, cultural and environmental factors. Numerous reviews published in recent years have highlighted the implication of genetic polymorphism on pain perception and response to drug therapy [103, 104]. The relevance of pharmacogenetics in labour analgesia has been explored in two recent studies, that examined the effect of single nucleotide polymorphism (SNP) 304A>G, located in the opioid μ-receptor (*OPRM1*) gene, on the response to intrathecal fentanyl in parturients in labour [105, 106]. This SNP, where an adenine is substituted for a guanine at the nucleotide position 118 in the *OPRM1* gene, has generated interest in that it may influence pharmacological and physiological responses to opioids. A detailed description of the pathophysiological and clinical implications of this mutation and others is provided in an excellent review by Landau and Kraft [107].

In a randomly allocated controlled trial, Landau et al. compared the ED_{50} of intrathecal fentanyl as part of a CSE for labour analgesia between two groups of 224 healthy nulliparous women with uncomplicated pregnancy [105]. Group A consisted of wild-type homozygote (304A) patients whereas group G included heterozygotes and homozygotes carrying the mutant 304G allele. The ED_{50} for fentanyl in group A, determined by an up-down sequential allocation method, was 26.8 μg (95% CI 22.7–30.9), compared to 17.7 μg (95% CI 13.4–21.9) in group G. Moreover, patients in group G (lower ED_{50}) requested supplemental analgesia at a greater cervical dilation than patients in group A. This finding is a counterintuitive result because increasing cervical dilation has been demonstrated to correlate with greater epidural analgesic requirements. These results suggest that this 304A>G mutation in the *OMPR1* gene may not only affect the potency of intrathecal fentanyl for labour analgesia, but also modulate pain tolerance. In a comparable population, Wong et al. investigated the effect of this same mutation on the duration of analgesia following a 25-μg intrathecal dose of fentanyl for labour [106]. There was no difference in any of the measured outcomes except for a lower incidence of pruritus in group G.

It follows from these two trials that the 304A>G SNP probably influences the pharmacodynamics of intrathecal fentanyl. However, the clinical significance of this single mutation on the overall response to spinal fentanyl administered for labour-induced pain is probably minimal. Several other SNPs have been and will be identified, which may potentially influence the pharmacokinetics and pharmacodynamics of neuraxially administered drugs (local anaesthetics, opioids, other adjuvants). Many more prospective randomised clinical trials will be necessary to elucidate their importance. Labour pain is a complex and multifactorial phenomenon. We are still far from seeing clinical applications from these studies but we believe that a thorough knowledge and understanding of pharmacogenetics is likely to help obstetric anaesthetists in the future to tailor analgesic therapy to suit patients' needs.

Breastfeeding

The benefits of breastfeeding on neonates' and infants' wellbeing are well established. Breast milk provides adequate nutrients to the newborn while protecting the baby against infectious disease, improving neonatal cognitive development and enhancing maternal-infant bonding. Successful breastfeeding is, however, dependant upon numerous factors and concerns that its initiation may be hindered by neuraxial analgesia has been extensively debated over the years [108–111]. Strong evidence that epidural labour analgesia, especially neuraxial opioids, affects initiation of breastfeeding is lacking, as the bulk of scientific literature on this subject is limited by its retrospective, observational or non-randomised nature. Several authors have highlighted the paucity of prospective, randomised controlled trials assessing the influence of epidural opioids on breastfeeding [112–114]. Although the review of neuraxial labour analgesia's influence on breastfeeding is beyond the scope of this article, we consider it important to discuss two articles, that are the only prospective, randomised controlled trials investigating the effect of neuraxial fentanyl administered during labour on breastfeeding.

Beilin et al. randomly allocated 177 healthy multiparous parturients with uncomplicated pregnancy into three groups during labour: epidural labour analgesia with (i) no fentanyl; (ii) intermediate-dose fentanyl (150 μg or less); and (iii) high-dose fentanyl (more than 150 μg) [115]. The investigators examined several breastfeeding and neonatal outcomes. The rate of difficulties with breastfeeding at 24 h postpartum was similar between the groups whether the mothers or the lactation consultants reported these difficulties. However, at 6 weeks postpartum, a telephone questionnaire revealed that significantly more mothers in the high-dose group reported difficulties with breastfeeding. This finding was correlated with a higher umbilical cord fentanyl concentration and higher maternal report of difficulty breastfeeding at 24 h postpartum. It is noteworthy that the failure rate of breastfeeding at 6 weeks was low and over 10% of participants were lost to follow-up at 6 weeks. This failure rate may, therefore, have introduced a bias that would warrant caution in interpreting these results. Indeed, had all the patients answered the questionnaire, it is possible that such a statistical difference would not appear between the groups.

More recently, Wilson et al. published a trial in which 1054 healthy nulliparous pregnant women with uncomplicated pregnancy were randomly allocated to receive high-dose bupivacaine-only labour epidural (control), low-dose bupivacaine with fentanyl labour epidural, CSE with fentanyl, or no neuraxial labour analgesia (of these 351 patients, 151 received parenteral

pethidine and 200 patients received other forms of analgesia or none at all) [116]. Among many obstetric and anaesthetic outcomes, the authors collected data on breastfeeding within 2–48 h and 12 months postpartum. They showed that the rate of initiating breastfeeding was the lowest among mothers who received pethidine for labour analgesia. There was no difference in the breastfeeding initiation rate between the epidural groups overall and the 'no neuraxial technique/no pethidine' patients. Moreover, there was no correlation between the total dose of neuraxial fentanyl and the breastfeeding initiation rate. Epidural labour analgesia and neuraxial fentanyl did not affect the length of breastfeeding.

These two prospective randomly allocated controlled trials provide the only available strong evidence that epidural labour analgesia and neuraxial fentanyl do not significantly affect breastfeeding. Indeed, none of these studies could demonstrate that epidural fentanyl impeded initiation of breastfeeding. Although Beilin et al. demonstrated that a cumulative dose of neuraxial fentanyl above 150 μg correlated with a 6-week decrease in breastfeeding, the overall success rate of breastfeeding in this study remained high. Furthermore, such an association was not observed by Wilson et al. Considering the available evidence so far, we conclude that low-dose local anaesthetic/low-dose fentanyl epidural labour analgesia regimens (as is the current practice in many obstetric anaesthesia centres) do not clinically affect breastfeeding and should be still offered to mothers wishing to breastfeed their babies.

Conclusion

One of the advances in modern anaesthesia is the integration of computer programs and ultrasonography into obstetric anaesthesia practice. These tools will certainly help obstetric anaesthetists enhance the quality and safety of their practice by reducing the risk of complications from neuraxial analgesia placement and drug administration. For instance, infusion pumps will be equipped with improved software, which will allow a more refined, complex and retroactive delivery of epidural analgesic solutions to meet mothers' increasing requirements as labour progresses. Ultrasound guided placement of epidural needles and catheters may become a standard of care just as it is for the siting of central venous catheters in the UK. In parallel with these technological improvements, recent studies evaluating epidural analgesic drug therapy suggest that new drugs – or should we say old drugs used in a new clinical context – might be introduced into the epidural analgesia regimens of the future. Before these innovations gain widespread acceptance among obstetric anaesthetists, further research is needed to assess and confirm their safety. Nevertheless, they offer great possibilities and opportunities for improved labour analgesia and maternal satisfaction during the exceptional experience of giving birth.

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Conflict of interest

No conflict of interest declared.

References

1 Dowswell T, Bedwell C, Lavender T, Neilson JP. Transcutaneous electrical nerve stimulation (TENS) for pain relief in labour. *Cochrane Database of Systematic Reviews* 2009; **15**(2): CD007214.
2 Smith CA, Collins CT, Cyna AM, Crowther CA. Complementary and alternative therapies for pain management in labour. *Cochrane Database of Systematic Reviews* 2006; **18**(4): CD003521.
3 Dickinson JE, Paech MJ, McDonald SJ, Evans SF. Maternal satisfaction with childbirth and intrapartum analgesia in nulliparous labour. *Australian and New Zealand Journal of Obstetric and Gynaecology* 2003; **43**: 463–8.
4 Anim-Somuah M, Smyth R, Howell C. Epidural versus non-epidural or no analgesia in labour. *Cochrane Database of Systematic Reviews* 2005; **19**(4): CD000331.
5 Carvalho JC. Ultrasound-facilitated epidurals and spinals in obstetrics. *Anesthesiology Clinics* 2008; **26**: 145–58, vii–viii.
6 Grau T, Leipold RW, Fatehi S, Martin E, Motsch J. Real-time ultrasonic observation of combined spinal-epidural anaesthesia. *European Journal of Anaesthesiology* 2004; **21**: 25–31.
7 Arzola C, Davies S, Rofaeel A, Carvalho JC. Ultrasound using the transverse approach to the lumbar spine provides reliable landmarks for labor epidurals. *Anesthesia and Analgesia* 2007; **104**: 1188–92.

8 Balki M, Lee Y, Halpern S, Carvalho JC. Ultrasound imaging of the lumbar spine in the transverse plane: the correlation between estimated and actual depth to the epidural space in obese parturients. *Anesthesia and Analgesia* 2009; **108**: 1876–81.
9 Vallejo MC, Phelps AL, Singh S, Orebaugh SL, Sah N. Ultrasound decreases the failed labor epidural rate in resident trainees. *International Journal of Obstetric Anesthesia* 2010; **19**: 373–8.
10 Grau T, Bartusseck E, Conradi R, Martin E, Motsch J. Ultrasound imaging improves learning curves in obstetric epidural anesthesia: a preliminary study. *Canadian Journal of Anesthesia* 2003; **50**: 1047–50.
11 Blanshard HJ, Cook TM. Use of combined spinal-epidural by obstetric anaesthetists. *Anaesthesia* 2004; **59**: 922–3.
12 Rawal N. Combined spinal-epidural anaesthesia. *Current Opinion in Anesthesiology* 2005; **18**: 518–21.
13 Preston R. The role of combined spinal epidural analgesia for labour: is there still a question? *Canadian Journal of Anesthesia* 2007; **54**: 9–14.
14 Arendt K, Segal S. Why epidurals do not always work. *Reviews in Obstetric & Gynecology* 2008; **1**: 49–55.
15 Cortes CA, Sanchez CA, Oliveira AS, Sanchez FM. Labor analgesia: a comparative study between combined spinal-epidural anesthesia versus continuous epidural anesthesia. *Revista Brasileira de Anestesiologia* 2007; **57**: 39–51.
16 Goodman SR, Smiley RM, Negron MA, Freedman PA, Landau R. A randomized trial of breakthrough pain during combined spinal-epidural versus epidural labor analgesia in parous women. *Anesthesia and Analgesia* 2009; **108**: 246–51.
17 Kayacan N, Ertugrul F, Cete N, et al. Comparison of epidural and combined spinal-epidural analgesia in the management of labour without pain. *Journal of International Medical Research* 2006; **34**: 596–602.
18 Norris MC. Are combined spinal-epidural catheters reliable? *International Journal of Obstetric Anesthesia* 2000; **9**: 3–6.
19 Thomas JA, Pan PH, Harris LC, Owen MD, D'Angelo R. Dural puncture with a 27-gauge Whitacre needle as part of a combined spinal-epidural technique does not improve labor epidural catheter function. *Anesthesiology* 2005; **103**: 1046–51.
20 Vernis L, Duale C, Storme B, Mission JP, Rol B, Schoeffler P. Perispinal analgesia for labour followed by patient-controlled infusion with bupivacaine and sufentanil: combined spinal-epidural vs. epidural analgesia alone. *European Journal of Anaesthesiology* 2004; **21**: 186–92.
21 Simmons SW, Cyna AM, Dennis AT, Hughes D. Combined spinal-epidural versus epidural analgesia in labour. *Cochrane Database of Systematic Reviews* 2007; **18**(3): CD003401.
22 Stocks GM, Hallworth SP, Fernando R, England AJ, Columb MO, Lyons G. Minimum local analgesic dose of intrathecal bupivacaine in labor and the effect of intrathecal fentanyl. *Anesthesiology* 2001; **94**: 593–8.
23 Graf BM, Zausig Y, Zink W. Current status and clinical relevance of studies of minimum local-anaesthetic concentration (MLAC). *Current Opinion in Anesthesiology* 2005; **18**: 241–5.
24 Columb MO, Lyons G. Determination of the minimum local analgesic concentrations of epidural bupivacaine and lidocaine in labor. *Anesthesia and Analgesia* 1995; **81**: 833–7.
25 Camorcia M, Capogna G, Columb MO. Minimum local analgesic doses of ropivacaine, levobupivacaine, and bupivacaine for intrathecal labor analgesia. *Anesthesiology* 2005; **102**: 646–50.
26 Sia AT, Goy RW, Lim Y, Ocampo CE. A comparison of median effective doses of intrathecal levobupivacaine and ropivacaine for labor analgesia. *Anesthesiology* 2005; **102**: 651–6.
27 Van de Velde M, Dreelinck R, Dubois J, et al. Determination of the full dose-response relation of intrathecal bupivacaine, levobupivacaine, and ropivacaine, combined with sufentanil, for labor analgesia. *Anesthesiology* 2007; **106**: 149–56.
28 Parpaglioni R, Frigo MG, Lemma A, Sebastiani M, Barbati G, Celleno D. Minimum local analgesic dose: effect of different volumes of intrathecal levobupivacaine in early labor. *Anesthesiology* 2005; **103**: 1233–7.
29 Okutomi T, Saito M, Mochizuki J, Kuczkowski KM. Combined spinal-epidural analgesia for labor pain: best timing of epidural infusion following spinal dose. *Archives of Gynecology and Obstetrics* 2009; **279**: 329–34.
30 Whitty R, Goldszmidt E, Parkes RK, Carvalho JC. Determination of the ED95 for intrathecal plain bupivacaine combined with fentanyl in active labor. *International Journal of Obstetric Anesthesia* 2007; **16**: 341–5.
31 Parpaglioni R, Frigo MG, Sebastiani M, Lemma A, Barbati G, Celleno D. High volume of subarachnoid levobupivacaine decreases drug requirement in first stage labor analgesia. *Minerva Anestesiologica* 2004; **70**: 809–21.
32 Lim Y, Ocampo CE, Sia AT. A comparison of duration of analgesia of intrathecal 2.5 mg of bupivacaine, ropivacaine, and levobupivacaine in combined spinal epidural analgesia for patients in labor. *Anesthesia and Analgesia* 2004; **98**: 235–9.
33 Suzuki N, Koganemaru M, Onizuka S, Takasaki M. Dural puncture with a 26-gauge spinal needle affects spread of epidural anesthesia. *Anesthesia and Analgesia* 1996; **82**: 1040–2.
34 Bernards CM, Kopacz DJ, Michel MZ. Effect of needle puncture on morphine and lidocaine flux through the spinal meninges of the monkey in vitro. Implications for

combined spinal-epidural anesthesia. *Anesthesiology* 1994; **80**: 853–8.
35 Cappiello E, O'Rourke N, Segal S, Tsen LC. A randomized trial of dural puncture epidural technique compared with the standard epidural technique for labor analgesia. *Anesthesia and Analgesia* 2008; **107**: 1646–51.
36 Nakamura G, Ganem EM, Rugolo LM, Castiglia YM. Effects on mother and fetus of epidural and combined spinal-epidural techniques for labor analgesia. *Revista da Associação Médica Brasileira* 2009; **55**: 405–9.
37 Van de Velde M, Teunkens A, Hanssens M, Vandermeersch E, Verhaeghe J. Intrathecal sufentanil and fetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. *Anesthesia and Analgesia* 2004; **98**: 1153–9.
38 Skupski DW, Abramovitz S, Samuels J, Pressimone V, Kjaer K. Adverse effects of combined spinal-epidural versus traditional epidural analgesia during labor. *International Journal of Gynecology and Obstetrics* 2009; **106**: 242–5.
39 Miro M, Guasch E, Gilsanz F. Comparison of epidural analgesia with combined spinal-epidural analgesia for labor: a retrospective study of 6497 cases. *International Journal of Obstetric Anesthesia* 2008; **17**: 15–9.
40 Moschini V, Marra G, Dabrowska D. Complications of epidural and combined spinal-epidural analgesia in labour. *Minerva Anestesiologica* 2006; **72**: 47–58.
41 Norris MC, Fogel ST, Conway-Long C. Combined spinal-epidural versus epidural labor analgesia. *Anesthesiology* 2001; **95**: 913–20.
42 Sia AT, Camann WR, Ocampo CE, Goy RW, Tan HM, Rajammal S. Neuraxial block for labour analgesia – is the combined spinal epidural (CSE) modality a good alternative to conventional epidural analgesia? *Singapore Medical Journal* 2003; **44**: 464–70.
43 Abrao KC, Francisco RP, Miyadahira S, Cicarelli DD, Zugaib M. Elevation of uterine basal tone and fetal heart rate abnormalities after labor analgesia: a randomized controlled trial. *Obstetrics and Gynecology* 2009; **113**: 41–7.
44 Landau R, Carvalho B, Wong C, Smiley R, Tsen L, Van de Velde M. Elevation of uterine basal tone and fetal heart rate abnormalities after labor analgesia: a randomized controlled trial. *Obstetrics and Gynecology* 2009; **113**: 1374.
45 Mardirosoff C, Dumont L, Boulvain M, Tramer MR. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. *British Journal of Obstetrics and Gynaecology* 2002; **109**: 274–81.
46 Cascio M, Pygon B, Bernett C, Ramanathan S. Labour analgesia with intrathecal fentanyl decreases maternal stress. *Canadian Journal of Anesthesia* 1997; **44**: 605–9.
47 Scull TJ, Hemmings GT, Carli F, Weeks SK, Mazza L, Zingg HH. Epidural analgesia in early labour blocks the stress response but uterine contractions remain unchanged. *Canadian Journal of Anesthesia* 1998; **45**: 626–30.
48 Segal S, Csavoy AN, Datta S. The tocolytic effect of catecholamines in the gravid rat uterus. *Anesthesia and Analgesia* 1998; **87**: 864–9.
49 Clarke VT, Smiley RM, Finster M. Uterine hyperactivity after intrathecal injection of fentanyl for analgesia during labor: a cause of fetal bradycardia? *Anesthesiology* 1994; **81**: 1083.
50 Van de Velde M. Combined spinal-epidural analgesia in labor. *Anesthesiology* 2000; **92**: 869–70.
51 Asokumar B, Newman LM, McCarthy RJ, Ivankovich AD, Tuman KJ. Intrathecal bupivacaine reduces pruritus and prolongs duration of fentanyl analgesia during labor: a prospective, randomized controlled trial. *Anesthesia and Analgesia* 1998; **87**: 1309–15.
52 Moore JM. Continuous spinal anesthesia. *American Journal of Therapeutics* 2009; **16**: 289–94.
53 Arkoosh VA, Palmer CM, Yun EM, et al. A randomized, double-masked, multicenter comparison of the safety of continuous intrathecal labor analgesia using a 28-gauge catheter versus continuous epidural labor analgesia. *Anesthesiology* 2008; **108**: 286–98.
54 Imbelloni LE, Gouveia MA. Continuous spinal anesthesia with Spinocath for obstetric analgesia. *International Journal of Obstetric Anesthesia* 2006; **15**: 171–2.
55 Turker G, Gurbet A, Aksu HA. Continuous spinal analgesia in parturients with severe heart disease. *International Journal of Obstetric Anesthesia* 2007; **16**: 297–9.
56 Gambling DR, Yu P, Cole C, McMorland GH, Palmer L. A comparative study of patient controlled epidural analgesia (PCEA) and continuous infusion epidural analgesia (CIEA) during labour. *Canadian Journal of Anaesthesia* 1988; **35**: 249–54.
57 van der Vyver M, Halpern S, Joseph G. Patient-controlled epidural analgesia versus continuous infusion for labour analgesia: a meta-analysis. *British Journal of Anaesthesia* 2002; **89**: 459–65.
58 Hawkins JL, Arens JF, Bucklin BA, et al. Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. *Anesthesiology* 2007; **106**: 843–63.
59 Hogan Q. Distribution of solution in the epidural space: examination by cryomicrotome section. *Regional Anesthesia and Pain Medicine* 2002; **27**: 150–6.
60 Halpern SH, Carvalho B. Patient-controlled epidural analgesia for labor. *Anesthesia and Analgesia* 2009; **108**: 921–8.
61 Paech MJ. Patient-controlled epidural analgesia in labour – is a continuous infusion of benefit? *Anaesthesia and Intensive Care* 1992; **20**: 15–20.
62 Boselli E, Debon R, Cimino Y, Rimmele T, Allaouchiche B, Chassard D. Background infusion is not beneficial during labor patient-controlled analgesia

with 0.1% ropivacaine plus 0.5 microg/ml sufentanil. *Anesthesiology* 2004; **100**: 968–72.
63 Lim Y, Ocampo CE, Supandji M, Teoh WH, Sia AT. A randomized controlled trial of three patient-controlled epidural analgesia regimens for labor. *Anesthesia and Analgesia* 2008; **107**: 1968–72.
64 Okutomi T, Saito M, Mochizuki J, Amano K, Hoka S. A double-blind randomized controlled trial of patient-controlled epidural analgesia with or without a background infusion following initial spinal analgesia for labor pain. *International Journal of Obstetric Anesthesia* 2009; **18**: 28–32.
65 Srivastava U, Gupta A, Saxena S, et al. Patient controlled epidural analgesia during labour: effect of addition of background infusion on quality of analgesia & maternal satisfaction. *Indian Journal of Anaesthesia* 2009; **53**: 649–53.
66 Vallejo MC, Ramesh V, Phelps AL, Sah N. Epidural labor analgesia: continuous infusion versus patient-controlled epidural analgesia with background infusion versus without a background infusion. *Journal of Pain* 2007; **8**: 970–5.
67 Missant C, Teunkenst A, Vandermeersch E, Van de Velde M. Patient-controlled epidural analgesia following combined spinal-epidural analgesia in labour: the effects of adding a continuous epidural infusion. *Anaesthesia and Intensive Care* 2005; **33**: 452–6.
68 Bremerich DH, Waibel HJ, Mierdl S, et al. Comparison of continuous background infusion plus demand dose and demand-only parturient-controlled epidural analgesia (PCEA) using ropivacaine combined with sufentanil for labor and delivery. *International Journal of Obstetric Anesthesia* 2005; **14**: 114–20.
69 Petry J, Vercauteren M, Van Mol I, Van Houwe P, Adriaensen HA. Epidural PCA with bupivacaine 0.125%, sufentanil 0.75 microgram and epinephrine 1/800.000 for labor analgesia: is a background infusion beneficial? *Acta Anaesthesiologica Belgica* 2000; **51**: 163–6.
70 Ferrante FM, Rosinia FA, Gordon C, Datta S. The role of continuous background infusions in patient-controlled epidural analgesia for labor and delivery. *Anesthesia and Analgesia* 1994; **79**: 80–4.
71 Campbell DC, Breen TW, Halpern SH, Muir H, Nunn R. RCT comparing the efficacy of PCEA alone vs PCEA + CIEA for ambulatory labor analgesia. *Anesthesiology* 2004; **101** (Suppl.): A1210.
72 Thénoz N, Boselli E, Sotian A, Bryssine B, Chassard D. Role of background infusion during labor PCEA with 0.0625% levobupivacaine Plus 0.5 μg/mL sufentanil. *Anesthesiology* 2006; **105**: A919.
73 Smiley RM, Stephenson L. Patient-controlled epidural analgesia for labor. *International Anesthesiology Clinics* 2007; **45**: 83–98.
74 Lim Y, Sia AT, Ocampo CE. Comparison of computer integrated patient controlled epidural analgesia vs. conventional patient controlled epidural analgesia for pain relief in labour. *Anaesthesia* 2006; **61**: 339–44.
75 Sia AT, Lim Y, Ocampo CE. Computer-integrated patient-controlled epidural analgesia: a preliminary study on a novel approach of providing pain relief in labour. *Singapore Medical Journal* 2006; **47**: 951–6.
76 Sng BL, Sia AT, Lim Y, Woo D, Ocampo C. Comparison of computer-integrated patient-controlled epidural analgesia and patient-controlled epidural analgesia with a basal infusion for labour and delivery. *Anaesthesia and Intensive Care* 2009; **37**: 46–53.
77 Capogna G, Celleno D, Lyons G, Columb M, Fusco P. Minimum local analgesic concentration of extradural bupivacaine increases with progression of labour. *British Journal of Anaesthesia* 1998; **80**: 11–3.
78 Bernard JM, Le Roux D, Frouin J. Ropivacaine and fentanyl concentrations in patient-controlled epidural analgesia during labor: a volume-range study. *Anesthesia and Analgesia* 2003; **97**: 1800–7.
79 Bernard JM, Le Roux D, Vizquel L, et al. Patient-controlled epidural analgesia during labor: the effects of the increase in bolus and lockout interval. *Anesthesia and Analgesia* 2000; **90**: 328–32.
80 Carvalho B, Cohen SE, Giarrusso K, Durbin M, Riley ET, Lipman S. ''Ultra-light'' patient-controlled epidural analgesia during labor: effects of varying regimens on analgesia and physician workload. *International Journal of Obstetric Anesthesia* 2005; **14**: 223–9.
81 Gambling DR, Huber CJ, Berkowitz J, et al. Patient-controlled epidural analgesia in labour: varying bolus dose and lockout interval. *Canadian Journal of Anaesthesia* 1993; **40**: 211–7.
82 Siddik-Sayyid SM, Aouad MT, Jalbout MI, et al. Comparison of three modes of patient-controlled epidural analgesia during labour. *European Journal of Anaesthesiology* 2005; **22**: 30–4.
83 Stratmann G, Gambling DR, Moeller-Bertram T, Stackpole J, Pue AF, Berkowitz J. A randomized comparison of a five-minute versus fifteen-minute lockout interval for PCEA during labor. *International Journal of Obstetric Anesthesia* 2005; **14**: 200–7.
84 Duncan LA, Fried MJ, Lee A, Wildsmith JA. Comparison of continuous and intermittent administration of extradural bupivacaine for analgesia after lower abdominal surgery. *British Journal of Anaesthesia* 1998; **80**: 7–10.
85 Scott DB, Schweitzer S, Thorn J. Epidural Block in postoperative pain relief. *Regional Anesthesia and Pain Medicine* 1982; **7**: 135–9.
86 Chua SM, Sia AT. Automated intermittent epidural boluses improve analgesia induced by intrathecal fentanyl during labour. *Canadian Journal of Anesthesia* 2004; **51**: 581–5.

87 Fettes PD, Moore CS, Whiteside JB, McLeod GA, Wildsmith JA. Intermittent vs continuous administration of epidural ropivacaine with fentanyl for analgesia during labour. *British Journal of Anaesthesia* 2006; **97**: 359–64.
88 Leo S, Ocampo CE, Lim Y, Sia AT. A randomized comparison of automated intermittent mandatory boluses with a basal infusion in combination with patient-controlled epidural analgesia for labor and delivery. *International Journal of Obstetric Anesthesia* 2010; **19**: 357–64.
89 Lim Y, Sia AT, Ocampo C. Automated regular boluses for epidural analgesia: a comparison with continuous infusion. *International Journal of Obstetric Anesthesia* 2005; **14**: 305–9.
90 Sia AT, Lim Y, Ocampo C. A comparison of a basal infusion with automated mandatory boluses in parturient-controlled epidural analgesia during labor. *Anesthesia and Analgesia* 2007; **104**: 673–8.
91 Wong CA, Ratliff JT, Sullivan JT, Scavone BM, Toledo P, McCarthy RJ. A randomized comparison of programmed intermittent epidural bolus with continuous epidural infusion for labor analgesia. *Anesthesia and Analgesia* 2006; **102**: 904–9.
92 Kaynar AM, Shankar KB. Epidural infusion: continuous or bolus? *Anesthesia and Analgesia* 1999; **89**: 534.
93 UK COMETCSG. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* 2001; **358**: 19–23.
94 Eisenach JC. Epidural neostigmine: will it replace lipid soluble opioids for postoperative and labor analgesia? *Anesthesia and Analgesia* 2009; **109**: 293–5.
95 Paech M, Pan P. New recipes for neuraxial labor analgesia: simple fare or gourmet combos? *International Journal of Obstetric Anesthesia* 2009; **18**: 201–3.
96 Roelants F, Lavand'homme PM, Mercier-Fuzier V. Epidural administration of neostigmine and clonidine to induce labor analgesia: evaluation of efficacy and local anesthetic-sparing effect. *Anesthesiology* 2005; **102**: 1205–10.
97 Van de Velde M, Berends N, Kumar A, et al. Effects of epidural clonidine and neostigmine following intrathecal labour analgesia: a randomised, double-blind, placebo-controlled trial. *International Journal of Obstetric Anesthesia* 2009; **18**: 207–14.
98 Dewandre PY, Kirsch M, Bonhomme V, Columb M, Hans P, Brichant JF. Impact of the addition of sufentanil 5 microg or clonidine 75 microg on the minimum local analgesic concentration of ropivacaine for epidural analgesia in labour: a randomized comparison. *International Journal of Obstetric Anesthesia* 2008; **17**: 315–21.
99 Dewandre PY, Decurninge V, Bonhomme V, Hans P, Brichant JF. Side effects of the addition of clonidine 75 microg or sufentanil 5 microg to 0.2% ropivacaine for labour epidural analgesia. *International Journal of Obstetric Anesthesia* 2010; **19**: 149–54.
100 Wallet F, Clement HJ, Bouret C, et al. Effects of a continuous low-dose clonidine epidural regimen on pain, satisfaction and adverse events during labour: a randomized, double-blind, placebo-controlled trial. *European Journal of Anaesthesiology* 2010; **27**: 441–7.
101 Parker RK, Connelly NR, Lucas T, et al. Epidural clonidine added to a bupivacaine infusion increases analgesic duration in labor without adverse maternal or fetal effects. *Journal of Anesthesia* 2007; **21**: 142–7.
102 Ross VH, Pan PH, Owen MD, et al. Neostigmine decreases bupivacaine use by patient-controlled epidural analgesia during labor: a randomized controlled study. *Anesthesia and Analgesia* 2009; **109**: 524–31.
103 Argoff CE. Clinical implications of opioid pharmacogenetics. *Clinical Journal of Pain* 2010; **26**(Suppl. 10): S16–20.
104 Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. *Clinical Pharmacology and Therapeutics* 2007; **81**: 429–44.
105 Landau R, Kern C, Columb MO, Smiley RM, Blouin JL. Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. *Pain* 2008; **139**: 5–14.
106 Wong CA, McCarthy RJ, Blouin J, Landau R. Observational study of the effect of mu-opioid receptor genetic polymorphism on intrathecal opioid labor analgesia and post-cesarean delivery analgesia. *International Journal of Obstetric Anesthesia* 2010; **19**: 246–53.
107 Landau R, Kraft JC. Pharmacogenetics in obstetric anesthesia. *Current Opinion in Anesthesiology* 2010; **23**: 323–9.
108 Chang ZM, Heaman MI. Epidural analgesia during labor and delivery: effects on the initiation and continuation of effective breastfeeding. *Journal of Human Lactation* 2005; **21**: 305–14.
109 Jordan S, Emery S, Watkins A, Evans JD, Storey M, Morgan G. Associations of drugs routinely given in labour with breastfeeding at 48 hours: analysis of the Cardiff Births Survey. *British Journal of Obstetrics and Gynaecology* 2009; **116**: 1622–9.
110 Torvaldsen S, Roberts CL, Simpson JM, Thompson JF, Ellwood DA. Intrapartum epidural analgesia and breastfeeding: a prospective cohort study. *International Breastfeeding Journal* 2006; **1**: 24.
111 Wieczorek PM, Guest S, Balki M, Shah V, Carvalho JC. Breastfeeding success rate after vaginal delivery can be high despite the use of epidural fentanyl: an observational cohort study. *International Journal of Obstetric Anesthesia* 2010; **19**: 273–7.
112 Devroe S, De Coster J, Van de Velde M. Breastfeeding and epidural analgesia during labour. *Current Opinion in Anesthesiology* 2009; **22**: 327–9.

113 Jordan S. Infant feeding and analgesia in labour: the evidence is accumulating. *International Breastfeeding Journal* 2006; **1**: 25.
114 Macfarlane A, Young S, Agaram R. Impaired breast-feeding and labour epidurals – is there really a link? *Anaesthesia* 2007; **62**: 750.
115 Beilin Y, Bodian CA, Weiser J, et al. Effect of labor epidural analgesia with and without fentanyl on infant breast-feeding: a prospective, randomized, double-blind study. *Anesthesiology* 2005; **103**: 1211–7.
116 Wilson MJ, MacArthur C, Cooper GM, Bick D, Moore PA, Shennan A. Epidural analgesia and breastfeeding: a randomised controlled trial of epidural techniques with and without fentanyl and a non-epidural comparison group. *Anaesthesia* 2010; **65**: 145–53.
117 Lim Y, Chakravarty S, Ocampo CE, Sia AT. Comparison of automated intermittent low volume bolus with continuous infusion for labour epidural analgesia. *Anaesthesia and Intensive Care* 2010; **38**: 894–9.
118 Sa Peixoto J, Celestino C, Fernandes N, Marques A, Pascoal I. Comparison of two techniques of epidural analgesia in the experience of labour: intermittent bolus versus continuous infusion. (ABSTRACT 11AP1-9). *European Journal of Anaesthesiology* 2010; **27**: 165.