Reports of Original Investigations

Intrathecal plain vs hyperbaric bupivacaine for labour analgesia: efficacy and side effects

[Bupivacaine intrathécale pure vs hyperbare pour l'analgésie du travail obstétrical : efficacité et effets secondaires]

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Purpose: Baricity is an important determinant of block characteristics of the spinal component of a combined spinal epidural (CSE) for labour analgesia. This study compares the analgesic efficacy and side effects of intrathecally administered plain and hyperbaric bupivacaine (both with fentanyl) during active labour.

Methods: Sixty-two women in active labour (cervical dilatation ≥ 5 cm and pain score > 5) were randomized in a prospective, single-blinded fashion to receive 2.5 mg of either hyperbaric or plain bupivacaine both combined with 15 μ g of fentanyl as the spinal component of a CSE. The primary outcome was failure of satisfactory analgesia within ten minutes of the intrathecal injection as defined by a verbal pain score > 3 . Secondary outcomes included need for rescue analgesia, hypotension, respiratory depression, nausea and vomiting, pruritus and sustained fetal bradycardia.

Results: Sixty patients were analyzed. The failure rates were 20% in the hyperbaric group vs 0% in the plain group ($P = 0.024$). The plain solution provided faster onset, higher sensory levels and less motor block at all times during the first 30 min. The incidence of both pruritus and sustained fetal bradycardia was 33% in the plain group and 10% in the hyperbaric group ($P = 0.03$).

Conclusion: A plain rather than hyperbaric solution of bupivacaine 2.5 mg with fentanyl 15 μ g provides a faster onset of analgesia, higher sensory levels and less motor block, while demonstrating an increased incidence of pruritus and sustained fetal bradycardia.

Objectif: La baricité modifie de façon importante les caractéristiques du bloc rachidien d'une rachi-péridurale combinée (RPC) pour l'analgésie du travail obstétrical. Cette étude compare l'efficacité analgésique et les effets secondaires de la bupivacaine pure à la bupivacaine hyperbare (les deux ajoutées à du fentanyl) en administration rachidienne pendant le travail obstétrical actif.

Méthode : Soixante-deux femmes en travail actif (dilatation cervicale ≥ 5 cm et échelle de douleur > 5) ont été randomisées de façon prospective et à simple insu à recevoir 2,5 mg de bupivacaine, soit pure, soit hyperbare, combinée à 15 μ g de fentanyl comme constituant rachidien d'une RPC. Le point d'aboutissement primaire était l'échec d'une analgésie satisfaisante dans les dix minutes suivant l'injection intrathécale, tel que défini par un pointage de douleur verbal > 3 . Les points d'aboutissements secondaires comprenaient la nécessité d'une analgésie de secours, la présence d'hypotension, une dépression respiratoire, des nausées et des vomissements, du prurit et une bradycardie fœtale soutenue.

Résultats : Soixante patientes ont été analysées. Le taux d'échec fut de 20 % dans le groupe hyperbare vs 0 % dans le groupe pur ($P = 0,024$). La solution pure a procuré un début d'analgésie plus rapide, des niveaux sensitifs plus élevés ainsi que moins de bloc moteur en tout temps durant les 30 premières minutes. L'incidence de prurit et de bradycardie fœtale soutenue fut de 33 % dans le groupe pur et de 10 % dans le groupe hyperbare ($P = 0,03$).

Conclusion : Une solution de 2,5 mg de bupivacaine pure plutôt qu'hyperbare avec 15 μ g de fentanyl fournit un début plus rapide d'analgésie, des niveaux sensitifs plus élevés et moins de bloc moteur, tout en provoquant une incidence plus grande de prurit et de bradycardie fœtale soutenue.

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COMBINED spinal epidural (CSE) provides effective and timely labour analgesia, particularly for women in active labour who are very distressed.^{1,2} In active labour, the ideal analgesic mixture should deliver rapid onset of satisfactory analgesia while minimizing side effects. The initial characteristics of the block are mainly determined by the doses of medications (local anesthetic and opioid) and the baricity of the intrathecal solution.^{3,4}

Compared to plain solutions, hyperbaric solutions might provide a more predictable block with fewer side effects, such as high block, hypotension, nausea, vomiting and pruritus.⁵ The use of hyperbaric solutions might risk ineffective analgesia from insufficient cephalad spread, however.⁶ Literature guiding the choice of baricity of intrathecal solutions is conflicting and lacks evidence for both potential benefits and adverse effects. This study compares the analgesic efficacy and side effects of plain and hyperbaric bupivacaine both with fentanyl as the intrathecal components of a CSE. It was hypothesized that a plain bupivacaine and fentanyl solution provides more effective analgesia than hyperbaric bupivacaine and fentanyl while potentially resulting in more side-effects.

Methods

The study was conducted with Research Ethics Board approval and written informed consent in a prospective, single-blinded, randomized fashion. Sixty-two, ASA physical status I-II, full-term pregnant women were enrolled. All participants were in active labour with a cervical dilation ≥ 5 cm and a verbal pain score (VPS) > 5 on a scale of 0 to 10. Patients were included if they had a vertex presentation, singleton pregnancy and maternal age ≥ 18 yr. Patients were excluded for preterm or postdate labour, an inability to communicate in English, baseline fetal heart rate (FHR) abnormalities, suspected fetal congenital anomalies or significant maternal medical complication of pregnancy. Intra-study withdrawal criteria included patients remaining in the sitting position for more than five minutes after spinal administration due to difficulties with epidural, failure of spinal analgesia to provide any sensory levels or delivery within 30 min of the CSE.

Upon request for labour analgesia, patients were randomly allocated to receive either hyperbaric or plain intrathecal anesthetic solution. Patients were randomized according to a computer-generated list of random numbers which were placed in opaque sealed envelopes. Parturients in the hyperbaric group received 1 mL of 2.5 mg·mL⁻¹ bupivacaine in dextrose 2.75%, made by diluting 0.75% bupivacaine in 8.25% dex-

trose (Marcaine™, Hospira, St-Laurent, QC, Canada) 1:2 with sterile water. Parturients in the plain group received 2.5 mg of plain bupivacaine (1 mL of 0.25% bupivacaine; Sensorcaine™, AstraZeneca, Mississauga, ON, Canada). Fifteen micrograms of fentanyl (0.3 mL; Sandoz, Boucherville, QC, Canada) were added to each solution, achieving a total volume of 1.3 mL for each group.

All patients received an *iv* fluid bolus of 250 mL of lactated Ringer's solution. Combined spinal epidural was performed in the sitting position at the L3–4 or L4–5 interspace. A needle-through-needle technique (17G epidural Tuohy needle and 26G Whitacre needle, Kimberly-Clark, UT, USA) was used. The epidural space was identified by loss of resistance to air. With cephalad orientation of its orifice, the spinal needle was advanced through the epidural needle to puncture the dura. Once free flow of clear cerebrospinal fluid (CSF) was obtained, the spinal dose was injected over ten seconds. The epidural catheter was then inserted 3–4 cm into the epidural space and a negative aspiration test for CSF or blood was confirmed. After securing the epidural catheter, the parturient was promptly positioned supine with left lateral uterine displacement. Maternal vital signs and FHR (using external cardiotocography) were continuously monitored throughout labour according to institutional protocols.

No epidural test dose was used, and no epidural top-ups were given within the first ten minutes of the intrathecal injection. After these ten minutes, any patient with a VPS > 3 was offered additional analgesia as an epidural top-up of 5–10 mL 0.125% plain bupivacaine. Patients with a VPS ≤ 3 also received the same epidural top up if requested. For all study patients, patient controlled epidural analgesia using a mixture of 0.0625% bupivacaine with 2 μ g·mL⁻¹ of fentanyl was initiated 30 min after spinal injection.

Baseline maternal and labour demographics were collected. Failure of the CSE to provide satisfactory analgesia, defined as a VPS > 3 at ten minutes was chosen as the study's primary outcome. Time zero was defined as the time at completion of the intrathecal injection.

The following parameters were recorded at baseline before CSE, and at intervals of five, ten, 20, and 30 min after CSE: 1) maternal vital signs (blood pressure, pulse rate, oxygen saturation (SpO₂) and respiratory rate; 2) VPS (0 = no pain, 10 = worst pain); and 3) sensory block level to pinprick. Motor block was assessed at 30 min using the Bromage scale (0 = no motor impairment, 1 = unable to raise the extended leg, but flexes knees and feet, 2 = unable to flex the

TABLE I Maternal and labour demographics

	<i>Hyperbaric group</i> (<i>n</i> = 30)	<i>Plain group</i> (<i>n</i> = 30)
Age (yr)	30.7 ± 6.8	31.6 ± 4.4
Height (cm)	163 ± 6.6	160.9 ± 5.3
Weight (kg)	77 ± 12	71.8 ± 9.8
Gestational age (weeks)	39.6 ± 1	39.2 ± 1.3
Gravidity	2 (1, 2)	2 (1, 2)
Parity	1 (0, 1)	1 (0, 1)
Cervical dilation	5 (5, 6)	5 (5, 7)
<i>Membranes</i>		
Intact	15 (50%)	13 (43.3%)
Ruptured	15 (50%)	17 (56.7%)
Oxytocin use	3 (10%)	3 (10%)
Induction of labour	6 (20%)	5 (16.7%)
Time to lying down (min)	2.4 ± 0.6	2.8 ± 0.8
<i>Mode of delivery</i>		
SVD	22 (73.4%)	22 (73.4%)
Instrumental	4 (13.3%)	2 (6.6%)
Cesarean	4 (13.3%)	6 (20%)

Data are presented as mean ± SD, median (q1, q3), or number (%). SVD = spontaneous vaginal delivery.

TABLE II Verbal pain scores (VPS)

<i>Time</i>	<i>VPS</i>	<i>Hyperbaric group</i> (<i>n</i> = 30)	<i>Plain group</i> (<i>n</i> = 30)	<i>P value</i>
Baseline	4-6	1	1	1.00
	7-10	29	29	
5 min	0-3	19	30	< 0.0001
	4-6	7	0	
10 min	7-10	4	0	0.024
	0-3	24	30	
	4-6	5	0	
20 min	7-10	1	0	0.49
	0-3	28	30	
	4-6	2	0	
30 min	0-3	29	30	1.00
	4-6	1	0	

Comparisons by Fisher's exact test.

knee but flexes feet, 3 = complete block; unable to move the foot). Within the first 30 min after CSE, parturients were observed for hypotension (systolic blood pressure down 20% from baseline) and respiratory depression (rate < 8 breaths·min⁻¹, or SpO₂ < 92%). They were actively questioned regarding nausea and vomiting and pruritus. During the 30 min post-CSE, the incidence of sustained fetal bradycardias was recorded. Bradycardia was recorded for a FHR of < 100 beats·min⁻¹ for > 60 sec. The mode of delivery was noted along with its indication. Maternal and fetal adverse effects were managed according to our institutional protocols.

Statistical analysis

The primary outcome was failure of the CSE to provide satisfactory analgesia within ten minutes as defined by a VPS > 3. Secondary outcomes included need for rescue analgesia, hypotension, respiratory depression, nausea and vomiting, pruritus and sustained fetal bradycardia. The number of patients in each group (*n* = 30) was determined by a prospective power analysis (power of 80% and type I error of 5%, two-tailed Chi-square test) based on a pilot study by the investigators involving 30 patients (15 per group) which showed that the estimated incidence of CSE failure using plain and hyperbaric solutions was approximately 0% and 25% respectively. Descriptive statistics such as mean and standard deviation or median and interquartile range are reported for continuous data and frequencies and percentages for categorical data. Continuous outcome variables were analyzed using the Mann-Whitney nonparametric test and categorical variables using the Chi-square or Fisher's exact test, as appropriate. No adjustments were made for the multiplicity of endpoints. Probability (*P*) values < 0.05 were considered significant. Analysis was by intention-to-treat. All analyses were done in SAS 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Sixty-two women were approached and recruited between November 2004 and April 2005. Two patients met intra-study withdrawal criteria and were excluded from the study for deliveries within the first 30 min leaving 60 patients for analysis.

Maternal and labour demographics were similar in both groups (Table I). Six patients (20%) in the hyperbaric group, compared with none in the plain group, had a VPS > 3 at ten minutes (*P* = 0.024). Four of these patients received rescue analgesia compared with none in the plain group (*P* = NS). No patient with a VPS score ≤ 3 requested or received additional analgesia. The median basal VPS (10) was identical in both groups. Following CSE, the plain group experienced significantly lower VPS at five and ten minutes compared to the hyperbaric group (Table II). The plain solution was associated with significantly higher levels of sensory blockade at all recorded times as well as less motor block at 30 min (Table III). The incidence of pruritus and sustained fetal bradycardia were significantly higher in the plain group than in the hyperbaric group (Table IV). The incidence of hypotension, nausea and vomiting did not differ significantly between groups, nor was respiratory depression observed in either group.

TABLE III Block characteristics after combined spinal epidural

	Hyperbaric group (n = 30)	Plain group (n = 30)	P value
<i>Sensory block level</i>			
5 min	T10 (6, 11)	T8 (4, 10)	< 0.0001
10 min	T8 (6, 11)	T6 (4, 8)	< 0.0001
20 min	T7 (6, 11)	T6 (4, 9)	< 0.0001
30 min	T7 (6, 11)	T6 (4, 9)	< 0.001
<i>Motor block* (30 min)</i>			
0	10 (33)	29 (97)	< 0.0001
1	16 (53)	1 (3)	
2	2 (7)	0	
3	2 (7)	0	

Data are presented as median (minimum, maximum) or number (%). T = thoracic dermatome. *Bromage scale. Sensory levels compared by the Mann-Whitney non-parametric test, motor block compared by Fisher's exact test.

TABLE IV COMPLICATIONS

	Hyperbaric group (n = 26)	Plain group (n = 30)	P value
Hypotension	3 (10)	7 (23.3)	0.17*
Respiratory depression	0	0	1.0**
Nausea and vomiting	1 (3.3)	1 (3.3)	1.0**
Pruritus	3 (10)	10 (33.3)	0.03*
Sustained fetal bradycardia	3 (10)	10 (33.3)	0.03*

Data are presented as number (%). *Chi-square test. **Fisher's exact test.

Discussion

Practitioners choose CSE for patients in active labour because it can deliver rapid pain relief with minimal motor block. The present study demonstrates that the plain bupivacaine 0.25% provides superior pain relief compared to hyperbaric bupivacaine, but results in an increased incidence of pruritus and sustained fetal bradycardia.

Both groups had similar baseline pain scores and degrees of stimulated labour, but plain bupivacaine was associated with a more acute reduction of pain scores following CSE. Previous trials have found conflicting results. Comparing 10% dextrose and plain solutions of intrathecal sufentanil, Ferouz *et al.*⁶ reported diminished analgesic efficacy of the hyperbaric solution based on increased requirements for rescue epidural analgesia. Similarly, Gage *et al.*⁷ demonstrated the relative ineffectiveness of intrathecal sufentanil in 7.5% dextrose for labour analgesia. Teoh and Sia,⁸ using a similar patient population to our own, demonstrated comparable labour analgesia for hyperbaric and plain bupivacaine solutions with fentanyl. The authors

reported similar onset but longer duration of 2.5 mg of bupivacaine in 8% dextrose compared to plain bupivacaine. However, the investigators used a technique of separate sequential injections of fentanyl and bupivacaine in order not to hinder cephalad spread of fentanyl. This novel technique might explain how the hyperbaric solution evaluated in their study was more effective than previously reported.

Baricity, defined as intrathecal anesthetic solution density relative to CSF density, is a major determinant of the extent of subarachnoid blockade.^{9,10} The mean CSF density in term parturients is 1.00030 ± 0.00004 g·mL⁻¹.¹¹ Dextrose-free (plain) solutions of bupivacaine and opioids, usually referred to as being isobaric, are actually hypobaric at body temperature, with a density less than 1.00000 g·mL⁻¹.^{3,12-14} The slight hypobaricity of plain solutions relative to CSF (0.00060 g·mL⁻¹ of difference), could explain the rapid, high sensory block observed after administration of plain local anesthetics and lipid-soluble opioids.^{10,11,15-17} Moreover, this pattern of cephalad spread might facilitate the antinociceptive effects of intrathecal opioids through dual activation of spinal as well as supraspinal receptor sites of action,¹⁸ which in turn, might augment the quality of analgesia of plain local anesthetics. The cephalad spread of these hypobaric solutions should be more pronounced when administered to patients in the sitting position.

Hyperbaric solutions, when injected in the sitting position, tend to gravitate to dependent areas and might not reach the T10-L1 dermatomes in adequate concentrations to produce efficient labour analgesia.⁶ Though commonly resulting in a more limited sensory blockade than plain solutions,^{5,8} hyperbaric solutions have been shown to exhibit different patterns of dermatomal spread depending on the dextrose concentration and density.¹⁴ Hallworth *et al.*¹⁹ and McLeod²⁰ reported that the addition of dextrose to bupivacaine produces solutions of predictable density in a linear manner, whereas the addition of fentanyl results in minimal changes to the final density of hyperbaric solutions.

In the previously mentioned studies reporting diminished analgesic efficacy of hyperbaric bupivacaine, dextrose concentrations of 7.5%⁷ and 10%⁶ were used. The densities of these solutions would be expected to be at least 1.02424 g·mL⁻¹.²⁰ In contrast, the hyperbaric solution used in our study had a dextrose concentration of only 2.75% with an estimated density of 1.00514 g·mL⁻¹ according to Hallworth *et al.*¹⁹ and McLeod.²⁰ The use of this less hyperbaric solution might have facilitated cephalad spread of the local anesthetic-fentanyl solution and possibly explains its better analgesic efficacy.

The association between intrathecal plain opioid solutions and clinically significant pruritus is well documented in previous studies.^{6,7} Pruritus associated with intrathecal opioids might result from both segmental spinal and supraspinal actions.^{21,22} Rapid cephalad spread rather than systemic absorption with redistribution to the brain possibly causes the pruritus and hypotension seen with solutions of lipophilic opioids and plain local anesthetics.^{6,7,23–26} Both our study and that of Paez *et al.*²⁷ support this explanation by showing less pruritus when fentanyl is combined with hyperbaric rather than plain bupivacaine. Although hypotension was not statistically different between both groups in our study, a trend towards hypotension requiring treatment was detected in parturients receiving the plain solution.

A significantly higher incidence of sustained fetal bradycardia was observed in patients receiving plain solutions. The study supports existing evidence that sustained fetal bradycardia is a recognized side-effect of the CSE technique for labour analgesia.^{28–32} Fortunately, post CSE fetal bradycardia is not associated with adverse neonatal outcomes.^{33,34} Most studies present a causal relationship between fetal bradycardia and the administration of intrathecal opioids, mainly sufentanil^{16,34,35} and fentanyl.^{31,36} One explanation of rapid analgesia induced fetal bradycardia is uterine hyperactivity due to a transient decrease in epinephrine levels, since baseline levels have a uterine relaxation effect via β -2 adrenergic receptors.^{31,37}

Previous studies fail to show appreciable differences in the incidence of FHR changes between hyperbaric and plain intrathecal solutions.^{7,8} Although sustained fetal bradycardia was a secondary outcome in our study, our results might support the hypothesis that rapid analgesia triggers fetal bradycardia after a CSE.^{32,35} The incidence of non-reassuring FHR changes increasingly reported in the literature,^{33,34,37} should prompt studies comparing intrathecal plain and hyperbaric solutions for labour analgesia powered to test for FHR changes as a primary outcome measure. A lower dose of local anesthetic in plain solutions might help to control this unwanted side effect.

While all personnel involved in a study should be blinded to group assignments, this is not always clinically practical. Parturients were blinded to the study solution but the investigator was not. Given the high level of distress of women in active labour, we felt that a double-blinded approach would have resulted in significant delays and practical difficulties recruiting patients. Furthermore, to have pre-prepared blinded syringes was not an option available in this study. To overcome this blinding limitation, an objective measure of efficacy, the VPS, was used.

In conclusion, this study demonstrates that a plain rather than hyperbaric solution of 2.5 mg bupivacaine with fentanyl 15 μ g provides faster analgesia, higher sensory levels and less motor block, yet is associated with an increased incidence of pruritus and sustained fetal bradycardia. The performance of the hyperbaric solution was improved compared to previous studies, by decreasing the dextrose concentration, hence the degree of hyperbaricity. These results demonstrate that the CSE used for active labour might provide a faster and more extensive block at the expense of side-effects such as motor block, pruritus, hypotension and fetal bradycardia. Moreover, the 2.5 mg dose of intrathecal plain bupivacaine could be reduced. Alternative techniques might include administering hyperbaric solutions in the lateral position. Studies are planned to further explore these strategies.

References

- 1 Cook TM. Combined spinal-epidural techniques. *Anaesthesia* 2000; 55: 42–64.
- 2 Rawal N, Holmstrom B, Crowhurst JA, Van Zundert A. The combined spinal-epidural technique. *Anesthesiol Clin North America* 2000; 18: 267–95.
- 3 Schiffer E, Van Gessel E, Fournier R, Weber A, Gamulin Z. Cerebrospinal fluid density influences extent of plain bupivacaine spinal anesthesia. *Anesthesiology* 2002; 96: 1325–30.
- 4 Eisenach JC. Combined spinal-epidural analgesia in obstetrics. *Anesthesiology* 1999; 91: 299–302.
- 5 Hocking G, Wildsmith JA. Intrathecal drug spread. *Br J Anaesth* 2004; 93: 568–78.
- 6 Ferouz F, Norris MC, Arkoosh VA, Leighton BL, Boxer LM, Corba RJ. Baricity, needle direction, and intrathecal sufentanil labor analgesia. *Anesthesiology* 1997; 86: 592–8.
- 7 Gage JC, D'Angelo R, Miller R, Eisenach JC. Does dextrose affect analgesia or the side effects of intrathecal sufentanil? *Anesth Analg* 1997; 85: 826–30.
- 8 Teoh WH, Sia AT. Hyperbaric bupivacaine 2.5 mg prolongs analgesia compared with plain bupivacaine when added to intrathecal fentanyl 25 microg in advanced labor. *Anesth Analg* 2003; 97: 873–7.
- 9 Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesth Analg* 1985; 64: 715–30.
- 10 Blomqvist H, Nilsson A. Is glucose-free bupivacaine isobaric or hypobaric? *Reg Anesth* 1989; 14: 195–8.
- 11 Richardson MG, Wissler RN. Density of lumbar cerebrospinal fluid in pregnant and nonpregnant humans. *Anesthesiology* 1996; 85: 326–30.
- 12 Richardson MG, Wissler RN. Densities of dextrose-free intrathecal local anesthetics, opioids, and combinations

- measured at 37 degrees C. *Anesth Analg* 1997; 84: 95–9.
- 13 *Lui AC, Polis TZ, Cicutti NJ*. Densities of cerebrospinal fluid and spinal anaesthetic solutions in surgical patients at body temperature. *Can J Anaesth* 1998; 45: 297–303.
- 14 *Connolly C, McLeod GA, Wildsmith JA*. Spinal anaesthesia for caesarean section with bupivacaine 5 mg ml(-1) in glucose 8 or 80 mg ml(-1). *Br J Anaesth* 2001; 86: 805–7.
- 15 *Stienstra R, van Poorten JF*. The temperature of bupivacaine 0.5% affects the sensory level of spinal anaesthesia. *Anesth Analg* 1988; 67: 272–6.
- 16 *Cohen SE, Cherry CM, Holbrook RH Jr, el-Sayed YY, Gibson RN, Jaffe RA*. Intrathecal sufentanil for labor analgesia--sensory changes, side effects, and fetal heart rate changes. *Anesth Analg* 1993; 77: 1155–60.
- 17 *Campbell DC, Camann WR, Datta S*. The addition of bupivacaine to intrathecal sufentanil for labor analgesia. *Anesth Analg* 1995; 81: 305–9.
- 18 *Crisp T, Stafinsky JL, Perni VC, Uram M*. The noradrenergic component contributing to spinal fentanyl-induced antinociception is supraspinally mediated. *Gen Pharmacol* 1992; 23: 1087–91.
- 19 *Hallworth SP, Fernando R, Stocks GM*. Predicting the density of bupivacaine and bupivacaine-opioid combinations. *Anesth Analg* 2002; 94: 1621–4.
- 20 *McLeod GA*. Density of spinal anaesthetic solutions of bupivacaine, levobupivacaine, and ropivacaine with and without dextrose. *Br J Anaesth* 2004; 92: 547–51.
- 21 *Ballantyne JC, Loach AB, Carr DB*. Itching after epidural and spinal opiates. *Pain* 1988; 33: 149–60.
- 22 *Thomas DA, Williams GM, Iwata K, Kenshalo DR Jr, Dubner R*. The medullary dorsal horn. A site of action of morphine in producing facial scratching in monkeys. *Anesthesiology* 1993; 79: 548–54.
- 23 *Gourlay GK, Murphy TM, Plummer JL, Kowalski SR, Cherry DA, Cousins MJ*. Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. *Pain* 1989; 38: 253–9.
- 24 *Hamilton CL, Cohen SE*. High sensory block after intrathecal sufentanil for labor analgesia. *Anesthesiology* 1995; 83: 1118–21.
- 25 *D'Angelo R, Eisenach JC*. Severe maternal hypotension and fetal bradycardia after a combined spinal epidural anesthetic. *Anesthesiology* 1997; 87: 166–8.
- 26 *Shennan A, Cooke V, Lloyd-Jones F, Morgan B, de Swiet M*. Blood pressure changes during labour and whilst ambulating with combined spinal epidural analgesia. *Br J Obstet Gynaecol* 1995; 102: 192–7.
- 27 *Paez JC, Soto RG, Schultetus RR*. Impact of baricity of bupivacaine on intrathecal fentanyl-associated pruritus. *Anesthesiology* 2003; 99: A1198 (abstract).
- 28 *Eltzschig HK, Lieberman ES, Camann WR*. Regional anesthesia and analgesia for labor and delivery. *N Engl J Med* 2003; 348: 319–32.
- 29 *Mardirosoff C, Dumont L, Boulvain M, Tramer MR*. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. *BJOG* 2002; 109: 274–81.
- 30 *Norris MC*. Intrathecal opioids and fetal bradycardia: is there a link? *Int J Obstet Anesth* 2000; 9: 264–9.
- 31 *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.
- 32 *Gambling DR, Sharma SK, Ramin SM, et al*. A randomized study of combined spinal-epidural analgesia versus intravenous meperidine during labor: impact on cesarean delivery rate. *Anesthesiology* 1998; 89: 1336–44.
- 33 *Van de Velde M, Vercauteren M, Vandermeersch E*. Fetal heart rate abnormalities after regional analgesia for labor pain: the effect of intrathecal opioids. *Reg Anesth Pain Med* 2001; 26: 257–62.
- 34 *Van de Velde M, Teunckens 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. *Anesth Analg* 2004; 98: 1153–9.
- 35 *Nielsen PE, Erickson JR, Abouleish EI, Perriatt S, Sheppard C*. Fetal heart rate changes after intrathecal sufentanil or epidural bupivacaine for labor analgesia: incidence and clinical significance. *Anesth Analg* 1996; 83: 742–6.
- 36 *Palmer CM, Maciulla JE, Cork RC, Nogami WM, Gossler K, Alves D*. The incidence of fetal heart rate changes after intrathecal fentanyl labor analgesia. *Anesth Analg* 1999; 88: 577–81.
- 37 *Segal S, Csavoy AN, Datta S*. The tocolytic effect of catecholamines in the gravid rat uterus. *Anesth Analg* 1998; 87: 864–9.