Addition of bupivacaine 1.25 mg to fentanyl confers no advantage over fentanyl alone for intrathecal analgesia in early labour

[L'ajout de 1,25 mg de bupivacaine au fentanyl n'apporte aucun avantage sur le fentanyl seul pour l'analgesie intrathecale au debut de l'accouchement]

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Purpose: a) To evaluate the effect of adding 1.25 mg of bupivacaine to intrathecal fentanyl on the duration of analgesia in an Asian population and b) to examine if the baricity of the local anesthetic at this dose has any bearing on the duration and quality of block.

Methods: Forty-eight parturients in early labour received combined spinal epidural (CSE) analgesia to evaluate a) the effect of adding 1.25 mg of bupivacaine to intrathecal (IT) fentanyl 25 µg on the duration of analgesia and b) the effect of baricity of intrathecal local anesthetic on the duration and quality of the block. Patients were randomly allocated to receive: IT fentanyl 25 µg plus normal saline (Group f, n=16), IT fentanyl 25 µg plus plain bupivacaine 1.25 mg (Group f+pb, n=16) and IT fentanyl 25 µg plus heavy bupivacaine 1.25 mg (Group f+hb, n=16). The two components of the IT injectate (total of 2.25 mL) were given sequentially.

Results: Group f+hb had the lowest sensory dermatomal block (T7 vs T4 (Group f), T5 (Group f+pb), $P < 0.01$). There were no differences in the duration of analgesia and incidence of side effects among the groups.

Conclusion: We found no advantage of adding 1.25 mg bupivacaine to fentanyl 25 µg. At this dose, the baricity of bupivacaine has no effect on the duration of analgesia.

Objectif : a) Évaluer l'effet de l'ajout de 1,25 mg de bupivacaine au fentanyl intrathecal sur la durée de l'analgesie chez une population asiatique et b) vérifier si la baricité de cette dose d'anesthésique local a quelque influence sur la durée et la qualité de l'analgesie.

Méthode : Quarante-huit parturientes ont reçu, au début de l'accouchement, une analgesie rachidienne peridurale combinée (RPC) pour évaluer a) l'effet de l'addition de 1,25 mg de bupivacaine à l'administration intrathecale (IT) de 25 µg de fentanyl sur la durée de l'analgesie et b) l'effet de la baricité de l'anesthésique intrathecal local sur la durée et la qualité de l'analgesie. Les patientes ont été répar-

ties de façon aléatoire et ont reçu : 25 µg de fentanyl IT plus un soluté physiologique (Groupe f, n = 16), 25 µg de fentanyl IT plus 1,25 mg de bupivacaine simple (Groupe f+bs, n = 16) ou 25 µg de fentanyl IT plus 1,25 mg de bupivacaine hyperbare (Groupe f+bh, n = 16). Les deux composants de la dose IT injectée (2,25 mL au total) ont été donnés séquentiellement.

Résultats : Le Groupe f+bh a présenté le bloc sensoriel le plus bas (T7 vs T4 (Groupe f), T5 (Groupe f+bs), $P < 0,01$). La durée de l'analgesie et l'incidence d'effets secondaires n'ont présenté aucune différence intergroupe.

Conclusion : L'ajout de 1,25 mg de bupivacaine à 25 µg de fentanyl n'a présenté aucun avantage. À cette dose, la baricité de la bupivacaine n'a pas d'effet sur la durée de l'analgesie.

COMBINED spinal epidural (CSE) analgesia is an effective and accepted mode of providing pain relief in labour. Intrathecal (IT) fentanyl 25 µg has been shown to provide good analgesia in early labour.¹ Studies have suggested that the addition of a small amount of local anesthetic augments the effect of IT opioids by increasing the duration of the block and speeding the onset of analgesia.^{2,3} Lee *et al.* showed that, with bupivacaine, 1.25 mg produced a similar onset and quality of analgesia as 2.5 mg when added to fentanyl 25 µg intrathecally as part of CSE in the first stage of labour.⁴ The reduced dose resulted in less motor and sensory block, and also decreased the incidence of hypotension but had a shorter duration of analgesia.

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Although the effect of baricity of IT opioids has been studied, the effect of IT hyperbaric local anesthetics in labour analgesia is less known. The aim of this study is twofold: a) to evaluate the effect of adding 1.25 mg of bupivacaine to IT fentanyl 25 µg on the duration of analgesia in our Asian population and b) to examine if baricity of local anesthetic at this dose has any bearing on the duration and quality of the block.

Methods

Following approval by the hospital Ethics Committee, 48 ASA I and II nulliparous women, with a term singleton fetus in active early labour (cervical dilatation score less than 5 cm) were recruited. Written informed consent was obtained and upon request for analgesia, parturients were randomly allocated by the sealed envelope method to three groups: intrathecal fentanyl (David Bull Lab, Australia) 25 µg (Group f, $n=16$), intrathecal fentanyl 25 µg and 1.25 mg plain bupivacaine (Astrazeneca, Sweden) (Group f+pb, $n=16$), or intrathecal fentanyl 25 µg and 1.25 mg 'hyperbaric' bupivacaine (with 8% glucose, Astrazeneca, Sweden) (Group f+hb, $n=16$). Parturients with abnormal lie or breech, pregnancy induced hypertension or other significant medical problems were excluded. Women with a pain score of <30 on the 0–100 visual analogue scale (0=no pain, 100=worst pain imaginable) were also excluded.

CSE block was performed by the principal investigator (EHLL) in the sitting position using the midline approach at L3, 4 intervertebral space after prehydration with 500–1000 mL Hartman's solution. The epidural space was identified using the loss of resistance to saline technique with a 17G Weiss needle. A 120-mm 27G Whitacre needle (Durasafe BD, USA) was then passed through the epidural needle and correct placement of the tip in the subarachnoid space confirmed by free flow of cerebrospinal fluid. 25 µg of fentanyl were diluted with preservative free normal saline solution to a total volume of 2 mL and administered intrathecally over 30 sec. This was followed immediately by 0.25 mL of normal saline, plain 0.5% bupivacaine or hyperbaric 0.5% bupivacaine over ten seconds for Group f, Group f+pb and Group f+hb, respectively. All drugs were prepared by another investigator who was not involved in the intrathecal injection or the subsequent evaluation of the parturient. The intrathecal injection was accomplished with the aperture of the Whitacre needle directed cephalad. The epidural catheter was then positioned 2.5–3.0 cm in the epidural space and aspirated for blood but no drugs were administered via the catheter until the patient requested further analgesia. The patient was placed with the torso elevated at 15° for 30 min after

subarachnoid administration to minimize cephalad migration of hyperbaric bupivacaine.

The assessment of the parturient was done by the principal investigator. The preblock systolic blood pressure was measured with a right brachial non-invasive blood pressure monitor (Dinamap, Critikon, Florida, USA) in the 15° elevated position and monitored every five minutes for the first 30 min after spinal anesthesia. The extent of motor blockade was assessed using the modified Bromage scale: 0=able to move hip, knee, ankle, and toes; 1=unable to move hip, able to move knee, ankle and toes; 2=unable to move hip and knee, able to move ankle and toes; 3=unable to move hip, knee and ankle, able to move toes; 4=unable to move hip, knee, ankle or toes. A Bromage scale of 0 was ensured prior to CSE and the degree of motor block was assessed five, 15 and 30 min after the block. The level of sensory loss was ascertained by loss of sensation to cold with an ice pack five, 15 and 30 min after the block. Similarly, pain scores were assessed at five minutes, 15 min and 30 min after the intrathecal administration of the drugs. The presence of pruritus, nausea or vomiting, shivering and sedation were also assessed at the same time intervals. Sedation was graded as 0=none; 1=easily rousable by light touch; 2=rousable with loud speech and shaking; 3=rousable with painful stimulation; 4=not rousable by any means. The other side effects were noted as present or absent. Parturients who still experienced pain 15 min after spinal anesthesia were categorized as 'analgesic failure' and their epidural catheters injected with 3 mL aliquots of 0.2% ropivacaine. Fetal heart rate changes were monitored 30 min before and after subarachnoid drug administration by the on-call obstetrician (not involved in the study) and managed according to the existing labour ward protocol. Any changes requiring intervention such as drugs or emergency Cesarean section were noted as non-reassuring fetal status. Type I decelerations and variable decelerations that resolved spontaneously with patient in the left lateral position were not considered non-reassuring. The use of oxytocin prior to subarachnoid block was noted.

Hypotension was defined as a systolic blood pressure less than 90 mmHg and treated with 6 mg boluses of ephedrine. The side effects (shivering, nausea and pruritus) if they occurred, would be treated only when requested by the patient.

Prospective power analysis indicated that with $\alpha=0.05$ and $\beta=0.2$, 16 patients per group would be able to detect clinically significant ½ hour differences in the duration of analgesia between the three groups. Continuous data are expressed as mean $\pm$ SD and were compared using analysis of variance (ANOVA). Non-parametric data were

FIGURE 1 Duration of block *vs* drug combination. No significant difference between groups.

FIGURE 2 Highest sensory block *vs* drug combination. $P < 0.01$ between Group f+hb *vs* f and Group f+pb.

TABLE Analgesic failure and side effects of the different intrathecal drugs

	Group f (n=16)	Group f+hb (n=16)	Group f+pb (n=16)
Analgesic failure	1	0	0
Nausea and vomiting	0	2	0
Sedation	12	13	14
Pruritus	15	15	15
Shivering	6	1	6
Hypotension	1	2	1

All values expressed as *n*.

No significant differences were found between groups.

compared using the Kruskal-Wallis and Chi squared tests as appropriate. Pain scores were analyzed using analysis of variance for repeated measures. A P value of <0.05 was considered significant.

Results

Patient demographics were comparable in terms of weight, height and baseline blood pressure. The average weight of patients in Group f was 67.58 ± 13.4 kg *vs* 66.45 ± 6.74 kg (Group f+hb) and 66.87 ± 12.46 kg (Group f+pb). The initial blood pressure readings in all three groups were comparable: 128 ± 12 mmHg (Group f), 122 ± 11 mmHg (Group f+hb) and 127 ± 14 mmHg (Group f+pb). More patients in the hyperbaric bupivacaine group (nine *vs* five each in the other groups) tended to be on oxytocin at the point of

administration of the subarachnoid block but this was not statistically significant.

The duration of analgesia for Group f+hb was 129.5 ± 48.5 min *vs* 100.1 ± 57.2 min for Group f, and 100.4 ± 50.0 min for Group f+pb (Figure 1). This difference was not statistically significant. There was one anesthetic failure in Group f. Pain scores were not different between the three groups for all patients who obtained satisfactory pain relief (Figure 2). A distinct anesthetic level could be discerned for every patient. The median height of sensory block to cold for Group f+hb was T7, as opposed to T4 for Group f, and T5 for Group f+pb (Figure 3). The difference in block height between Group f+hb and the other two groups was statistically significant ($P < 0.01$), but not between Group f and Group f+pb.

There was no difference in the incidence of side effects (Table). None of fetal heart changes required emergent obstetric intervention. None of the parturients delivered before the request for epidural supplementation of analgesia.

Discussion

Our study shows that the addition of 1.25 mg bupivacaine does not confer any significant advantage to IT fentanyl 25 μ g in our Asian population. The duration of analgesia and the side effect profiles were indistinguishable among the three groups. This was consistent with the findings of another study which also demonstrated that the duration and quality of labour analgesia produced by IT fentanyl 25 μ g plus bupivacaine 1.25 mg was similar to IT fentanyl 25 μ g

FIGURE 3 Pain score *vs* time. No significant difference was found by ANOVA for repeated measures.

alone.² In that study, Palmer *et al.* showed that bupivacaine 2.5 mg but not 1.25 mg, in combination with fentanyl prolonged the duration of action without a significant increase in the incidence of side effects. In contradiction with Palmer's results, Lee *et al.* showed that when added to IT fentanyl 25 µg, bupivacaine 1.25 mg was as effective as 2.5 mg; but the latter dose of bupivacaine was associated with more side effects.⁴ However, the absence of a control group (that received IT fentanyl only) in the latter study questions the relevance of comparing their results with ours.

Intrathecal fentanyl 25 µg has been shown to provide adequate pain relief in the first stage of labour when used as the sole agent.¹ To improve the duration and quality of labour analgesia, particularly in the later part of the first stage of labour⁵ when the intensity of pain increases and the quality of the pain changes to assume a greater somatic component,⁶ various combinations of local anesthetics and opioids have been studied. Indeed, synergism between these two groups of drugs has been demonstrated.³ Studies in Asian women to exploit this synergistic relationship have resulted in an increase in the incidence of hypotension and motor blockade when IT 2.5 mg bupivacaine was used in combination with either fentanyl 25 µg or sufentanil 5 µg for labour analgesia.^{4,7} For this reason, we undertook the present study using a lower dose of IT bupivacaine although, eventually, this did not produce a significant degree of synergism. From this, we could infer that the use of an intermediate dose of IT bupivacaine (i.e., between 1.25 mg and 2.5 mg range)

may, theoretically, optimize the balance between analgesia and side effects.

Baricity refers to the ratio of the density of a solution to that of CSF measured at 37°C.⁸ It (with the effects of gravity determined by patient posture and the curves of the vertebral column) is recognized as an important factor in determining the spread of a solution when injected intrathecally. The effect of baricity on intrathecal opioids has been studied. Cage *et al.* demonstrated that the use of IT hyperbaric sufentanil administered in the sitting position shortened the duration of labour analgesia.⁹ Similarly, Kang *et al.* found that hyperbaric fentanyl administered intrathecally in a sitting position resulted in reduced quality and duration of labour analgesia.¹⁰ The underlying mechanism postulated is that dextrose restricts the cephalad spread of intrathecal opioid, thereby preventing sufficient concentrations from reaching the lower thoracic region of the spinal cord and brainstem where it binds to opioid receptors and produces the desired analgesic effect. In our investigation, we sought to study only the effects of hyperbaric bupivacaine and not hyperbaric fentanyl. Therefore, we administered the local anesthetic solution and the opioid separately, in an attempt to preserve the effects due to the baricity of the solutions. We intended that, with the parturients in the sitting position, the administration of IT fentanyl (being a hypobaric preparation)¹¹ first would allow sufficient amounts to reach the site of opioid action and would not be affected by the baricity of the subsequent injectate. This manoeuvre was successful, apparently, since all our patients in the hyperbaric bupivacaine group obtained adequate labour analgesia of at least the same quality and duration as the fentanyl and fentanyl plus plain bupivacaine groups despite a lower level of highest sensory block height. On the other hand, the effect of baricity of local anesthetics was evident from the lower levels of sensory blockade of the hyperbaric bupivacaine group when compared with the others. The finding that a distinct block height was obtained for all patients, even those who did not get bupivacaine, was not surprising as sensory changes in patients who received IT sufentanil¹² and IT fentanyl² alone have been reported previously. We were unable to determine if the quality of the sensory block was different between groups. We can only conclude that the duration and quality of analgesia produced was indistinguishable among the three groups in our study. We can also infer that, with the regimens described, the level of spinal blockade to cold is not an indication of the duration of analgesia.

Our study shows that the currently employed regimens were effective for early labour analgesia. There were also no serious side effects. As there was one case

of analgesic failure in the fentanyl only group, a further reduction of the dosage of IT fentanyl 25 µg should be undertaken cautiously as this could predispose to a higher analgesic failure rate. In this event, the rationale of performing dural puncture in the CSE technique may not be fully justified, as it is not without potential risks.¹³

In summary, our study indicated that there was no significant advantage of adding 1.25 mg of bupivacaine to fentanyl 25 µg intrathecally for women in early labour in our Asian population. There was also no significant advantage of administering hyperbaric bupivacaine intrathecally at the dose of 1.25 mg in early labour. We administered intrathecal drugs sequentially in an attempt to preserve the effects due to the baricity of the drugs. Further research is required to investigate the effects of higher intrathecal doses of hyperbaric bupivacaine and its use in late labour.

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