Singapore Med J 1998; Vol 39(7):290-294

The Addition of Intrathecal Sufentanil and Fentanyl to Bupivacaine for Caesarean Section

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ABSTRACT

Aim of Study: Intrathecal sufentanil has recently been used in labour as part of a combined spinal epidural technique. This study was conducted to compare its use in combination with bupivacaine for caesarean section with fentanyl added to bupivacaine and bupivacaine alone.

Methods: Sixty ASA I and II patients for non-emergency caesarean section under spinal anaesthesia were divided into three groups to receive 15 μg fentanyl added to 7.5 mg bupivacaine, 10 μg sufentanil added to 7.5 mg bupivacaine and 7.5 mg bupivacaine. Onset time of sensory blockade, side effects, surgical conditions, neonatal outcome and quality of the anaesthetic was assessed. On the first post-operative day, duration of effective analgesia, side effects and patient satisfaction were noted.

Results: The duration of effective analgesia of bupivacaine alone was prolonged with the addition of sufentanil and fentanyl by 358% and 256% respectively. No patient in the sufentanil and fentanyl groups required additional intra-operative analgesics compared with 17.6% of patients in the bupivacaine alone group. There was an increase in incidence of desaturation in the sufentanil group (45%) and fentanyl group (5.6%) compared with the bupivacaine only group (0%). The incidence of pruritus was 35% with sufentanil, 27.8% with fentanyl against 0% with bupivacaine alone.

Conclusion: The addition of 10 μg of sufentanil and 15 μg of fentanyl to 7.5 mg of bupivacaine prolonged the duration of effective analgesia and improved intra-operative analgesia. However, the incidence of pruritus and episodes of desaturation were increased more with 10 μg sufentanil than with 15 μg fentanyl.

Keywords: intrathecal sufentanil, fentanyl, bupivacaine, caesarean section

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INTRODUCTION

Spinal anaesthesia has increasingly become the technique of choice[1,2] for caesarean delivery. Spinal anaesthesia has the advantages of simplicity of technique[3,4], rapid onset of action and reliability in producing uniform sensory and motor blockade when compared to epidural anaesthesia[5,6,8]. Its main disadvantage relates to its limited duration of action and hence lack of long-lasting post-partum analgesia.

To address the problem of limited duration of action and to improve the quality of analgesia both intra-operatively and post-operatively, intrathecal opiates have been given in addition to bupivacaine[7-12].

Abboud[13] reported the use of mini-dose intrathecal morphine for the relief of post-caesarean section pain in 1988. 0.25 mg morphine given intrathecally with bupivacaine provided a mean duration of analgesia of approximately 28 hours. The risk of delayed respiratory depression of relatively hydrophilic opioids has prevented the widespread use of intrathecal morphine.

The use of intrathecal fentanyl, a lipophilic opioid, and bupivacaine for caesarean delivery was described by Hunt[7]. The addition of 6.25 μg fentanyl to bupivacaine for spinal anaesthesia was shown to improve intraoperative analgesia and to provide analgesia into the immediate postoperative period with no adverse effects on the mother or neonate.

Recently there has been interest in using intrathecal sufentanil, an even more lipophilic opioid, either alone or in combination with bupivacaine for labour analgesia[14-16]. Sufentanil alone provided analgesia in the first stage of labour for between 1 – 3 hours[15-17]. The use of intrathecal sufentanil in combination with bupivacaine for caesarean section has not been reported.

The aim of this study was to evaluate the addition of intrathecal sufentanil to bupivacaine for caesarean section and to compare its use to that of intrathecal fentanyl and bupivacaine.

METHODS

We studied 60 ASA I and II patients (American Society of Anesthesiologists grading system ASA I – a normal healthy individual, ASA II – a patient with mild systemic disease) undergoing non-emergency caesarean section under spinal anaesthesia. Informed consent was obtained from all patients and the study was approved by the Hospital Ethics Committee. The patients were randomly assigned to receive, in a prospective double-blind fashion, one of three test solutions. The anaesthetist performing the block would make up the study solution with instructions obtained from an envelope. After the administration of the study solution, the patients were evaluated by an investigator blinded to the test solution given.

In study group A, a solution consisting of 7.5 mg bupivacaine (1.5 mLs of 0.5% plain bupivacaine) and

15 μg of fentanyl (made up to 1.5 mLs) was diluted with preservative free 0.9% saline to a total volume of 4 mLs by the anaesthetist performing the block.

In study group B, a solution consisting of 7.5 mg bupivacaine (1.5 mLs of 0.5% plain bupivacaine) and 10 μg of sufentanil (made up to 1 mL) was diluted with 0.9% saline to a total volume of 4 mLs.

In study group C, a solution consisting of 7.5 mg bupivacaine (1.5 mLs of 0.5% plain bupivacaine) was diluted with 0.9% saline to a total volume of 4 mLs.

All patients received 30 mLs of sodium citrate pre-operatively. The patients were pre-loaded through a 16G cannula with 1000 mLs is of Hartman's balanced salt solution. The procedure was then performed under aseptic conditions with the patient in the left lateral position. The interspace between lumbar vertebrae 3 and 4 (L3/4) or the interspace between lumbar vertebrae 2 and 3 (L2/3) was chosen. The spinal anaesthetic was performed using a 20G introducer needle and a 27G (Becton-Dickenson) Whitacre spinal needle. After identification of clear, free flowing cerebrospinal fluid, the chosen study solution was injected slowly through the spinal needle. The patients were then turned onto a supine position with a left lateral tilt to effect uterine displacement. All patients were routinely given 40% supplemental oxygen via a ventimask until the baby was delivered.

The level of sensory blockade to cold was assessed with an ice pack in the mid-clavicular line. The time for the sensory blockade to reach T6 and T4 levels were recorded.

Caesarean section was only allowed to proceed when a sensory level of T4 was attained. Patients in whom sensory blockade did not reach T4 were excluded from the study.

The patients were monitored continuously with ECG and pulse oximetry. The blood pressure was recorded every 5 minutes for 120 minutes. Any fall in blood pressure greater than 20% decrease in mean arterial pressure or a systolic arterial pressure less than 90 mmHg systolic was treated with boluses of 6 mg of ephedrine and fluids where appropriate. All episodes of hypotension, nausea and vomiting, shivering, somnolence, respiratory depression, inadequate analgesia and pruritis were recorded. Any treatment given for side-effects was noted. The duration of surgery was noted.

The quality of the surgical conditions afforded was assessed by the operating surgeon on a three point scale. (1 – insufficient if unable to proceed with surgery; 2 – adequate if able to proceed but with some difficulty, and 3 – optimal operating conditions).

At the end of the caesarean section, the Apgar scores at 1 and 5 minutes assessed by the attending midwife were noted. Birth weight and gestational age were recorded on the first post-operative day.

At 120 mins after the block was given, the patients were assessed for their degree of somnolence using the Campbell score[17] (1 – wide awake; 2 – sedated but easily arousable; 3 – drowsy and difficult to arouse, and 4 – unarousable). Residual motor blockade was assessed using the Bromage scale[18]. (0 – unable to move feet or knees, 1 – moves feet only, 2 – moves feet and knees, and 3 – full range of movements). The patients were asked to assess the quality of the anaesthesia on a four-point modified Belzarena scale[9] (1 – unable to tolerate pain; 2 – able to tolerate discomfort with additional analgesia; 3 – some discomfort but no additional analgesics required, and 4 – completely satisfied).

On the first post-operative day, the patients were interviewed to check for headache, backache, nausea and vomiting and pruritis. The presence of urinary retention was not assessed as our patients are routinely catheterised for 24 hours post-operatively. Effective analgesia, defined as the time to request for the first dose of analgesia, was recorded. The patients were asked if they would choose the same form of anaesthesia should they require another caesarean section.

Parametric data were assessed for statistical significance using analysis of variance and Student-Newman-Keuls test for comparison between groups. Non-parametric data were assessed with the Chi-square test with Pearson correction. Differences were considered statistically significant when $p < 0.05$. SPSS for MS Windows Release 6.0 was used for statistical analysis.

RESULTS

There were no significant differences in patient age, weight, height, parity, ASA status or duration of surgery between the three groups (Table I).

Table I – Demographic data

Group	Fentanyl 15 μg + Bupivacaine 7.5 mg	Sufentanil 10 μg + Bupivacaine 7.5 mg	Bupivacaine 7.5 mg
Number of patients (n)	18	20	17
Maternal age (yr)	31.2 ± 4.6	31.2 ± 6.4	31.9 ± 4.6
Maternal weight (kg)	67.6 ± 9.3	72.9 ± 8.4	70.6 ± 12.2
Maternal height (cm)	155.2 ± 5.1	154.9 ± 7.0	156.7 ± 5.3
Parity			
Primiparous	6	9	8
Multiparous	12	11	9
ASA			
I	14	11	11
II	4	9	6
Surgical time (mins)	49.7 ± 13.7	47.1 ± 10.7	48.2 ± 17.7

Values are mean ± SD

Table II – Sensory blockade to T6 and T4 level

Group	Fentanyl 15 μg + Bupivacaine 7.5 mg	Sufentanil 10 μg + Bupivacaine 7.5 mg	Bupivacaine 7.5 mg
Number of patients (n)	18	20	17
T6 (seconds)	151.6 ± 76.4	145.0 ± 62.2	183.6 ± 49.3
T4 (seconds)	225.5 ± 123.7	196.9 ± 105.0	245.8 ± 91.0
Duration of effective analgesia (mins)	385.8 ± 307.4	540.1 ± 283.4	150.9 ± 103.4

Values are mean ± SD

Table III – Incidence (%) of side effects

Group	Fentanyl 15 μg + Bupivacaine 7.5 mg	Sufentanil 10 μg + Bupivacaine 7.5 mg	Bupivacaine 7.5 mg
Number of patients (n)	18	20	17
Desaturation	1 (5.6)	9 (45)	0 (0)
Pruritus	5 (27.8)	7 (35)	0 (0)
Nausea	4 (22.2)	5 (25)	2 (11.8)
Hypotension	14 (77.8)	17 (85)	12 (70.6)

Two patients in the fentanyl added to bupivacaine group and 3 patients in the bupivacaine group, were excluded from the study because a sensory level of T4 was not attained before 15 mins after intrathecal injection. This was due to difficulty in obtaining a good backflow of cerebrospinal fluid through the 27G Whitacre needle before intrathecal injection of the study solution. Surgery was then carried out under general anaesthesia.

There was no significant difference in onset of sensory blockade to T6 and T4 levels (Table II). All patients included in the study attained a T4 sensory level within 10 mins of intrathecal injection to allow surgery to proceed.

Duration of effective analgesia (Table II)

The duration of effective analgesia was defined as the time from intrathecal injection to the time of first request for analgesia. The duration of effective analgesia was 385.8 ± 307.4 mins with 15 μg of fentanyl added and 540.1 ± 283.4 mins with 10 μg sufentanil compared to 150.9 ± 103.4 mins for the bupivacaine 7.5 mg alone group. This represented an increase in the mean duration of effective analgesia of 256% for the fentanyl group and 358% for the sufentanil group compared to the bupivacaine alone group.

Quality of intra-operative analgesia

Three of the 17 (17.6%) patients in the bupivacaine alone group complained of pain intra-operatively and required intravenous fentanyl or pethidine intra-operatively after the delivery of the baby. No patients in the other two groups required additional analgesics intra-operatively.

Side-effects (Table III)

There was a significant increase in the incidence of pruritus with the addition of 10 μg of sufentanil to bupivacaine ($p = 0.028$). Thirty-five percent (7/20) of patients who received sufentanil complained of itching affecting the face and the upper body. Of these 7 patients, 2 required treatment for the itch. 27.8% (5/18) of patients who received 15 μg of fentanyl complained of itching affecting mainly the nose and face. No patients in the bupivacaine alone group complained of pruritus.

The incidence of desaturation, defined as a saturation below 94% with the patient breathing room air after the delivery of the baby, was significantly increased ($p = 0.0005$) with the addition of sufentanil. Forty-five percent (9/20) of patients in the sufentanil group had episodes of desaturation compared with 5.6% (1/18) in the fentanyl group and 0% in the bupivacaine only group.

Hypotension was defined as any fall greater than 20% in the mean arterial pressure or a systolic pressure less than 90 mmHg. These episodes of hypotension were treated with boluses of 6 mg of ephedrine and fluid loading. There was no significant difference between the three groups with respect to the incidence of hypotension.

Nausea was reported in 25% (5/20) in the sufentanil group, 22.2% (4/18) in the fentanyl group and 11.8% (2/17) in the bupivacaine alone group. There was no significant difference between the three groups.

There were no significant differences in the degree of somnolence or motor blockade 120 mins after intrathecal injection of the study solutions using the Kruskal-Wallis one-way Anova test. There was also no significant difference in the surgical conditions offered by the three test solutions as assessed by the principal operating surgeon.

Satisfaction

There was no significant difference in the patients assessment of intra-operative anaesthesia at 120 mins. When interviewed on the first post-operative day, 1 patient in the fentanyl group and 1 patient in the sufentanil group said that they would not choose the same anaesthetic again because they disliked the pain of the initial spinal injection. Two patients in the bupivacaine alone group said that they would not have

Table IV – Neonatal outcome

Group	Fentanyl 15 μg + Bupivacaine 7.5 mg	Sufentanil 10 μg + Bupivacaine 7.5 mg	Bupivacaine 7.5 mg
Number of patients (n)	18	20	17
Birth weight (g)	2790.2 ± 688.9	3087.5 ± 441.9	3032.6 ± 416.2
Gestation (wks)	36.9 ± 2.2	38.0 ± 1.5	38.2 ± 1.5
APGAR 1 min	8.9 ± 0.3	8.7 ± 0.9	8.4 ± 1.1
APGAR 5 mins	9.0 ± 0.0	9.0 ± 0.2	9.0 ± 0.0

Values are mean ± SD

the same anaesthetic again as they had more pain post-operatively when the block wore off compared to their previous experience with general anaesthesia for a previous caesarean section. All the remaining 51 (92.7%) patients were satisfied and would choose the same anaesthetic again should they have another caesarean section in the future.

All fetuses in the three groups were comparable in birth weight and gestational age. There was no significant difference in Apgar scores at 1 and 5 mins using analysis of variance with the Student-Newman-Keuls test (Table IV).

DISCUSSION

In this study it was demonstrated that the addition of 15 μg of fentanyl and 10 μg of sufentanil to bupivacaine intrathecally significantly prolonged the mean duration of effective analgesia by 256% and 358% respectively. 15 μg of fentanyl added to 7.5 mg bupivacaine provided effective analgesia for 6.43 hours and 10 μg of sufentanil added to 7.5 mg bupivacaine provided effective analgesia for 9.00 hours. This provided improved patient comfort and reduced the need for intra-muscular and intravenous analgesia in the immediate post-operative period.

There was a prolongation of effective analgesia and a significant improvement in intra-operative patient comfort with the addition of fentanyl and sufentanil to bupivacaine. 17.6% of patients in the bupivacaine only group complained of pain and were given additional intra-operative analgesics compared to no patients in the fentanyl and sufentanil groups. Intra-operative analgesia in the bupivacaine only group could be improved by using a higher dose of bupivacaine but this would increase the level of sensory blockade and the incidence of hypotension. The duration of motor blockade would also be prolonged.

Both fentanyl and sufentanil possess local anaesthetic properties which have been demonstrated *in vitro*[20] and clinically sensory changes have been reported with the use of intrathecal sufentanil and fentanyl[15,22]. This local anaesthetic property may contribute to the synergistic effect between fentanyl, sufentanil and bupivacaine. The exact mechanism however remains unclear. It has been suggested that by acting at different ionic channels, local anaesthetics blocking sodium channels and the opiates inhibiting voltage dependent calcium channels, there is a potentiation of the resulting inhibition of neuronal excitability[17].

Systemic opioid potencies correlate directly with opioid lipophilicity reflecting the need to cross the blood brain barrier to gain access to the receptor site. Therefore sufentanil (octanol/water partition coefficient 1778) is considered 10 times as potent as fentanyl (octanol/water partition coefficient 813) when systemically administered[17,20]. Intrathecal drugs bypass the blood-brain barrier and therefore their systemic potencies do not predict intrathecal potency. There have been few human studies on the potency ratios of intrathecal sufentanil and fentanyl, but Honet et al[20] estimated that after intrathecal injection, sufentanil is only twice as potent as fentanyl. The findings of this study support this estimate with the duration of effective analgesia provided by the addition of 10 μg of sufentanil being 1.4 times that of 15 μg of fentanyl compared to the expected 1.3 times if intrathecal sufentanil was twice as potent as fentanyl.

Hunt et al reported a more rapid onset of spinal block when subarachnoid fentanyl was added to bupivacaine for caesarean delivery[7]. Subsequent studies[8,20] did not demonstrate an enhancement in onset of spinal blockade when fentanyl and sufentanil were added to bupivacaine. In this study, there was no significant difference in onset of sensory blockade to T6 and T4. All patients included in the study attained a T4 level within 20 mins of intrathecal injection of the study solutions.

Recently, there has been an increase in the popularity of using intrathecal sufentanil in a combined spinal epidural technique for labour analgesia. Hays and Palmer[22] reported a case of early respiratory depression after administering 15 μg of intrathecal sufentanil during labour. In our study, we used 10 μg of sufentanil and 15 μg of fentanyl in addition to 7.5 mg of bupivacaine. The incidence of desaturations to below 94% was 45% for the sufentanil group and 5.6% for the fentanyl group with the patients breathing room air. No patients in the bupivacaine 7.5 mg group had any episode of desaturation. In all the patients, the episodes of desaturation were easily corrected by asking the patients to take a few deep breaths and by giving supplemental oxygen at 40%. At the end of the recovery monitoring period at 120 mins, no patient experienced any episode of desaturation. This finding is in agreement with Palmer who reported early respiratory depression occurring after intrathecal fentanyl-morphine combination[21] and intrathecal sufentanil[22] alone. Delayed onset of respiratory depression has not been reported for

the lipophilic opiates sufentanil[12] and fentanyl[9]. There was no difference in the degree of somnolence when the patients were assessed at 120 mins. We conclude that intrathecal sufentanil and fentanyl are safe for use. The patients should have their respiratory rates monitored every 15 mins for the first hour after injection and every 30 mins for the next 2 hours[22] with the addition of pulse oximetry and supplemental oxygen for those patients who have demonstrated episodes of desaturation intra-operatively.

When Leicht et al[23] compared the intrathecal use of 25 μg fentanyl and 10 μg sufentanil for labour analgesia, they found the incidence of pruritus to be 60% and 85% respectively. In our study, 27.8% of those who received 15 μg of fentanyl and 7.5 mg of bupivacaine had pruritus involving the nose and face. Thirty-five percent of those who received 10 μg of sufentanil and 7.5 mg of bupivacaine had pruritus involving the face and upper body. The pruritus was mild and transient in the fentanyl group, which did not require treatment. In the group who received sufentanil, 2 of the 7 patients who complained of pruritus required treatment with chlorpheniramine.

Cohen et al[15] reported an incidence of hypotension in 14% of subjects when intrathecal sufentanil was used for labour analgesia. However, Campbell et al[17] reported no increase in hypotension when intrathecal sufentanil was added to bupivacaine for labour analgesia. Belzarena[9] reported only mild hypotension which was easily treated with ephedrine when fentanyl was added to bupivacaine for caesarean section. In our study, the addition of fentanyl and sufentanil did not increase the incidence of hypotension. The episodes of hypotension were transient and responded to fluid loading or boluses of 6 mg of ephedrine.

Intrathecal fentanyl and bupivacaine for caesarean delivery and sufentanil for labour analgesia have both established an excellent safety record when neonatal Apgar scores, umbilical blood gases and neurobehavioural assessments were made[7,15]. The present study supports the established safety of adding fentanyl and sufentanil to bupivacaine in finding no significant difference in the Apgar scores of the neonates in all the three groups.

In summary, the addition of 10 μg of sufentanil and 15 μg of fentanyl to 7.5 mg of bupivacaine prolonged the duration of effective analgesia and improved intra-operative analgesia. However, the incidence of pruritus and episodes of desaturation were increased more with 10 μg sufentanil than with 15 μg fentanyl.

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