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Combined Spinal Epidural for Labour Analgesia – Duration, Efficacy and Side Effects of Adding Sufentanil or Fentanyl to Bupivacaine Intrathecally vs Plain Bupivacaine

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ABSTRACT

Aim of Study: The aim of the study was to evaluate the efficacy and side effects of adding sufentanil 10 μg, fentanyl 10 μg or a control of 1 mL saline to 2.5 mg bupivacaine given intrathecally via combined spinal epidural (CSE) for labour pain relief in the first stage.

Method: Sixty ASA I or II patients who requested for epidural analgesia were randomised to three groups. CSE was performed with a 16G Touhy needle and 27G Whitacre needle.

Results: Patients in the sufentanil/bupivacaine group had a significantly longer duration of analgesia (162.9 min ± 63.4) compared with fentanyl/bupivacaine (110.0 min ± 44.6) compared with plain bupivacaine (70.0 min ± 32.1). Pruritus was significant in patients with sufentanil (80%) and fentanyl (47.4%) but did not occur with plain bupivacaine. There was no significant difference in the incidence of nausea or vomiting, hypotension and motor blockade although blood pressures in the sufentanil group were consistently lower than the other two groups. Pain scores were lowest in the sufentanil group. Fetal heart rate changes and Apgar scores were not significantly different between the groups.

Conclusion: In combined spinal epidural for labour analgesia, adding sufentanil 10 μg to intrathecal bupivacaine 2.5 mg provided fast onset and good analgesia for a longer duration compared with adding fentanyl 10 μg and with plain bupivacaine. The main side effect was pruritus. Neonatal outcome was similar.

Keywords: anaesthesia: obstetric, anaesthetic technique: combined spinal epidural, analgesic: sufentanil, fentanyl

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INTRODUCTION

The CSE technique for obstetrics was first described for anaesthesia for Caesarean section whereby a rapid onset of anaesthesia was obtained which could then be continued via the epidural catheter if necessary[1]. It then became popular for providing analgesia in the first stage using small doses of lipophilic opioids such as fentanyl and sufentanil intrathecally which could provide analgesia without motor blockade. The main drawback for intrathecal sufentanil and fentanyl appear to be a limited duration of action. By combining opioid and low-dose bupivacaine, the duration and quality of analgesia can be prolonged without an increase in motor blockade[2]. The aim of this study is to compare the efficacy of intrathecal administration of 2 opioids (sufentanil 10 μg or fentanyl 10 μg) with a saline control when added to 2.5 mg of bupivacaine and to evaluate the duration of analgesia and side effects including cardiotocograph changes.

METHOD

Patients who requested for epidural analgesia in labour were recruited for the study. Patients were excluded if they had pre-eclampsia, received any parenteral opioids within the last 3 hours, pre-existing hypertension, non-gestational diabetes mellitus or any contraindication to regional anaesthesia. Informed consent was obtained. After preloading with 500 mLs Hartman's solution, all the patients received combined spinal epidural in the left lateral position at L3/4 by the midline approach. A 16G Touhy needle was used for the epidural and a 27G Whitacre spinal needle passed through the Touhy needle. Patients were excluded from the study if the spinal failed to show backflow of cerebrospinal fluid. They were randomised to three groups for the intrathecal injection: all patients received 5 mLs 0.05% bupivacaine to which was added, in Group C – 1 mL saline, Group F – 10 μg fentanyl in 1 mL saline, and in Group S – 10 μg sufentanil in 1 mL saline. After the intrathecal injection, an epidural catheter was threaded through the Touhy needle but no drugs were given epidurally

until the patient requested for pain relief. The duration of action of the intrathecal study solutions was considered to be the time from the intrathecal injection to when the patient requested for pain relief again.

All patients were assessed with a 10 point visual analogue scale for pain before the CSE and then at 5, 15 and 30 mins after the CSE as well as when they requested for further analgesia again. Blood pressure was monitored every 5 mins for 30 mins followed by 15 mins monitoring using non-invasive monitoring (Dinamap or Colins Pressmate). Patients were assessed at 5, 15 and 30 mins after the CSE for motor blockade using a modified Bromage[3] score and sensory level using a cold swab.

When patients requested for pain relief again after the intrathecal injection, they were given epidural analgesia. They were asked for the presence of pruritus, nausea or vomiting before any epidural drug was administered. A test dose of Lignocaine 1.5% 3 mLs or 0.25% bupivacaine 3 mLs was given followed by a bolus of 0.25% bupivacaine to obtain analgesia at the attending anaesthetist's discretion. This was followed by an infusion of 0.125% bupivacaine with fentanyl 2 μg/mL at a rate also decided upon by the attending anaesthetist.

All the patients and their obstetricians were blinded to the study solution. The cervical dilatation of the patient was assessed at the time of CSE and again when the epidural was required. All patients had cardiotocograph (CTG) monitoring. The CTG was assessed by an independent obstetrician for 3 hours after the CSE and compared with the CTG one hour before the CSE. A blinded assessor performed the Apgar scoring at 1 and 5 mins.

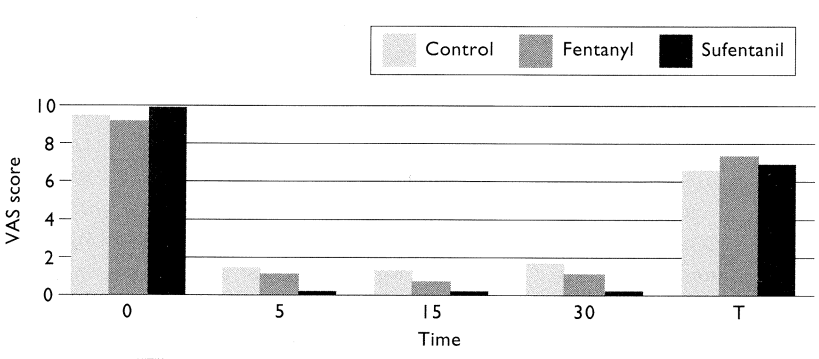
Statistical analysis was performed by analysis of variance, Kruskal-Wallis ANOVA test for non-parametric values and chi-squared test or Fisher's exact test with Yates correction.

RESULTS

There were 20 patients in each group. One patient in Gp F was excluded as she developed abruptio placentae and required emergency Caesarean section. There were no differences in the patient demographics with respect to age, weight and height. The proportion of primiparous to multiparous women in each of the groups did not differ significantly (Table I). The birthweight, Apgar scores and mode of delivery also did not vary significantly (Table II).

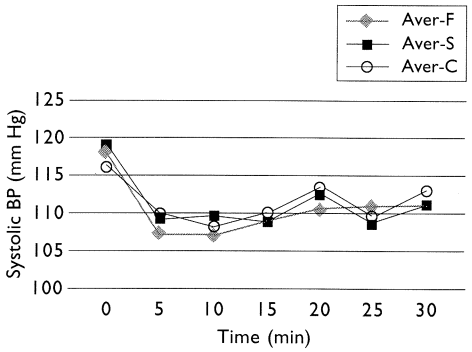
Patients in Gp S experienced the longest duration of analgesia after the CSE before requesting for further pain relief via the epidural catheter (Table III). Between groups, the difference was highly significant between Gp C and Gp S ($p < 0.001$), Gp F and Gp S ($p < 0.01$) and significant between Gp F and Gp C ($p < 0.05$) (Table III).

Mean VAS pain scores between groups were not significantly different before CSE (Time 0 in Fig 1) and again when they requested for further pain relief (Time T in Fig 1). At 5, 15 and 30 mins after the CSE, pain scores were lowest in Gp S and highest in Gp C. This was statistically significant at 30 mins between Gp S and C ($p < 0.001$) and between Gp F and Gp C ($p < 0.05$). The main side effect that was significant was pruritus (Table IV). Eighty percent of patients given sufentanil and 47.4% given fentanyl experienced this while none occurred in the control group. The incidences of nausea or vomiting and hypotension (decrease of more than 20% of systolic blood pressure from baseline) requiring ephedrine were not significantly different among the three groups. However, in each group, there was a decrease in systolic blood pressure following CSE (Fig 2) compared to the respective baseline blood pressure before CSE. Although the mean decrease was statistically significant ($p < 0.05$) within the first 30 mins in groups F and S, it was not clinically significant.



"T" refers to the time when the patients requested for further pain relief.

Fig 1 – VAS scores before and after CSE



F = Fentanyl, S = Sufentanil, C = Control

Fig 2 – Systolic blood pressure after CSE

The CTG changes were assessed to be normal, suspicious or ominous (Table IV)[4,5]. All the CTGs were normal before CSE was administered. The most common abnormalities were a silent pattern and variable deceleration. There were no significant differences in the number of suspicious or ominous fetal heart tracings (Table V) before epidural top-up was given. Two patients developed suspicious CTG associated with hypotension after CSE. These fetal heart rate changes were noted in the first hour after the CSE. One (Gp S) required Caesarean section for fetal distress while the other (Gp F) recovered but was later sectioned for dystocia. The other incidences of fetal heart rate changes did not warrant operative intervention. All except two from Gp S occurred in the first hour after CSE and recovered after that. The two patients from Gp S

Table I – Patient demographics

	Control n = 20	Fentanyl n = 19	Sufentanil n = 20
Age – yrs (SD)	27.8 (2.3)	28.1 (3.5)	27.1 (3.9)
Weight – kg (SD)	64.4 (7.4)	67.1 (7.8)	68.0 (8.3)
Height – cm (SD)	158.2 (6.0)	157.9 (4.6)	158.5 (4.7)
Primips	17	16	18
Multips	3	3	2

SD: standard deviation

Table II – Obstetrics outcome

	Control n = 20	Fentanyl n = 19	Sufentanil n = 20
Birthweight – gm (SD)	3159.8 (353.4)	3133.6 (340.9)	3252.3 (402.5)
median Apgar 1"	9	9	9
median Apgar 5"	9	9	9
Delivery mode			
NVD	11	7	7
Assisted	7	5	6
LSCS	2	7	7

Table III – Duration of analgesia*

Duration - mins	Control n = 20	Fentanyl n = 19	Sufentanil n = 20	p
Mean (SD)	70 (32.1)	111.9 (44.1)	169 (61.8)	< 0.0001
Range	25 – 145	30 – 215	90 – 285	-
95% CI	55 – 85	91 – 133	141 – 199	-

For patients who delivered without requesting for further pain relief, the duration of analgesia was assumed to be the time from CSE to the time of delivery. There was 1 such patient in Gp F and 3 in Gp S.

CI = Confidence interval

Table IV – Side effects

	Control n = 20	Fentanyl n = 19	Sufentanil n = 20	p
Pruritus	0	9 (47.4%)	16 (80%)	0.0004
Nausea/Vomiting	5 (25%)	3 (15.8%)	4 (20%)	ns
Ephedrine used (Hypotension)	5 (25%)	5 (26.3%)	4 (20%)	ns

Table V – CTG changes after the CSE but before epidural

	Control	Fentanyl	Sufentanil
Normal	17	15	16
Suspicious	3	4	3
Ominous	0	0	1
Total	20	19	20

developed suspicious fetal heart rate patterns more than 120 mins after CSE. The overall incidence of fetal heart rate changes after CSE was 18.6%.

Mean cervical dilatation was similar in all groups before CSE. The cervical dilatation had progressed more in Gp S (Gp S – 3.5 cm to 6.7 cm, Gp F – 3 cm to 6 cm and Gp C – 3.8 cm to 5.5 cm) by the time epidural top-up was requested but this was not statistically significant. Motor blockade assessed by modified Bromage score was not significantly different between groups. No patient had a score more than 2. At the end of 30 mins after CSE, 16 patients in Gp C, 17 in Gp F and 19 in Gp S had a Bromage score of zero, indicating the ability to perform straight-leg raising off the bed. Patients in the sufentanil group achieved the highest levels of sensory blockade. By 30 mins, the median sensory level to cold in Grp S reached T-3 dermatome while in Grp F, it reached T-4 and in Grp C it was T-8. The difference was significant between Grp C and Grp S ($p < 0.01$).

DISCUSSION

Epidural analgesia has been the gold standard for labour pain relief. Now, combined spinal epidural analgesia may be replacing this because of its rapid onset, reliability and lack of motor blockade when low dose bupivacaine and opioids are used.

The duration and quality of analgesia of low dose intrathecal bupivacaine is shown in this study to be enhanced by sufentanil 10 μg and fentanyl 10 μg. Low dose intrathecal bupivacaine alone is insufficient. At the doses used, adding sufentanil provided a significantly longer duration of analgesia with better visual analogue pain scores compared to adding fentanyl. A higher dose of fentanyl may provide a more comparable duration. However, currently there are no studies which compare intrathecal opioid potency ratios in parturients. Systemic potencies correlate directly with opioid lipophilicity because systemic opioids need to cross the blood brain barrier to act on opioid receptors. However, intrathecally injected drugs bypass the blood brain barrier and hence, their lipophilicity do not reflect their intrathecal potency. A recent study has established the ED 50 for intrathecal sufentanil in parturients at 2.6 (1.8 – 3.2 95% CI) μg and the ED 95 at 8.9 (7.5 – 11.5 95% CI) μg[6]. There are no published data regarding the dose response for intrathecal fentanyl. Intrathecal fentanyl has been used in doses ranging from 10 μg to 25 μg. The duration of analgesia in various studies have ranged from 81.6 $\pm$ 8.9 min using 10 μg of fentanyl to 129 $\pm$ 66 min using 25 μg fentanyl combined with 0.25 mg of morphine in an attempt to prolong the duration of analgesia[7,8].

Fetal heart tracing abnormalities with epidural analgesia have been reported to range from 7% to 25% and to be related to maternal hypotension and uterine hyperstimulation[11-13]. Nielsen et al compared intrathecal sufentanil with epidural bupivacaine and found that the incidence of clinically significant fetal heart rate abnormalities (21.5% vs 23.4%) and hypotension (18.5% vs 17.2%) was equivalent in both groups within the first hour of administration and there was a significantly higher risk of Caesarean section in patients whose previously normal fetal heart tracing became abnormal[14]. Cohen et al found significant fetal heart rate changes in 15% of patients in the first two hours after intrathecal sufentanil but none were clinically significant and none resulted in intervention for fetal compromise[15].

Our study is the first comparison of the effect of intrathecal low dose bupivacaine, with fentanyl

Table VI – CTG definition

	Suspicious CTG	Ominous CTG
Baseline heartrate	150 – 170 bpm or 100 – 110 bpm with normal variability, no decelerations; absence or accelerations for > 40 mins	Baseline heartrate >150 bpm with silent pattern and/or repetitive late or variable decelerations
Silent pattern	> 40 mins with normal baseline, no decelerations	for > 90 mins
Baseline variability	> 25 bpms in the absence of accelerations; variable decelerations of depth < 60 bpm, duration < 60s	Complicated variable decelerations of depth > 60 bpm, duration > 60s and changes in shape: overshoot, decreased or increased baseline heartrate following deceleration, or absence of baseline variability in or between decelerations, slow recovery; combined/biphasic decelerations. Repetitive late decelerations; pronounced loss of baseline variability regardless of baseline heartrate with shallow decelerations; sinusoidal pattern with no accelerations
Bradycardia	Occasional transient prolonged bradycardia if heartrate drops to < 80 bpm for > 2 mins or > 3 mins if < 100 bpm	Prolonged bradycardia in a suspicious trace; prolonged bradycardia > 10 min with no signs of recovery

or sufentanil on fetal heart tracing. The fetal heart rate changes which occurred after epidural top-up could be due to the effects of the epidural and hence only the changes which occurred in the time interval before top-up were considered. Our incidence of significant fetal heart rate changes at 18.6% is comparable although there are slight differences in the definitions used. In the two cases with hypotension, who developed suspicious CTG, the CTG changes were seen in the third hour after CSE (but before epidural top-up) whereas the hypotension occurred in the first 30 mins and was promptly treated and responded to fluids and ephedrine. In both cases, although they required Caesarean section, this was indicated more than seven hours after CSE. The indications for Caesarean section were dystocia in one patient and fetal distress in another. It would be difficult to conclude if the fetal distress had any relation to the CSE or the hypotension as presumably the CTG had recovered to be reassuring enough to continue labour for several hours. It is possible that more CTG changes could be detected in the fentanyl and sufentanil group by virtue of the fact that these groups had a longer duration of analgesia than the control group before epidural commenced since CTG changes after commencement of epidural were disregarded. However, the differences in the three groups were not significant despite this bias.

Both these opioids did not cause any significant increase in incidence of motor blockade and their combination with bupivacaine may thus be used for ambulatory labour analgesia. Sufentanil is known to cause sensory changes, sometimes inducing a very high block to sensation without the motor effects[9]. This is evidenced by the progression of sensory blockade to cold to a much higher level compared with fentanyl and plain bupivacaine. It is believed to be due to the direct effect of sufentanil on *mu* receptors in the spinal cord. Hypotension is commonly seen with epidural and spinal anaesthesia, due to sympathetic blockade by the action of local anaesthetic. It is also seen when only intrathecal sufentanil is given, thus probably the relief of pain itself plays a part in the decrease in blood pressure[10]. In this study, although the sufentanil group showed a consistently lower blood pressure, the incidence of clinically significant hypotension requiring ephedrine was similar in all three groups and probably reflects the effect of the low dose of bupivacaine.

Other side effects of nausea and vomiting and pruritus are well known for intrathecal opioids. The pruritus can be treated with intravenous nalbuphine or diphenhydramine but none of our patients required treatment as the effects were mild and tolerable. There have been some reports recently on respiratory depression associated with the use of intrathecal sufentanil in parturients[16,17]. Patients who have been given parenteral opioids shortly before receiving intrathecal opioids may be at an increased risk of respiratory depression. We took the precaution of excluding patients who had received pethidine intramuscularly within the last three hours. Although we did not assess sedation scores, none of our patients were noted to be excessively drowsy. However we recommend that patients be monitored for sedation and respiratory rates when using intrathecal opioids.

The effect of combined spinal epidural analgesia on labour outcome cannot be commented on in this study because a larger study population would be needed. There have been suggestions that the lack of motor blockade is advantageous in preventing malrotation of the fetal head during descent and therefore may lead to a less need for midcavity forceps. However this has yet to be borne out in any large scale studies. In addition, there are too many confounding factors once epidural commenced as the study was designed to look at the effects of CSE only and did not standardise for epidural techniques or obstetric indications for intervention.

CONCLUSION

Combined spinal epidural analgesia for first stage labour using low dose intrathecal bupivacaine provides rapid onset analgesia but requires enhancement of the duration and quality of analgesia with sufentanil or fentanyl. As with epidural analgesia, close attention must be paid to prevent hypotension. The incidence of fetal heart rate changes appear to be similar to other epidural techniques.

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