Comparative Study of Intrathecal Sufentanil Bupivacaine versus Intrathecal Bupivacaine in Patients Undergoing Elective Cesarean Section

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ABSTRACT

Background: Sufentanil added to intrathecal bupivacaine for cesarean section has shown to improve intraoperative and postoperative analgesia with no adverse effects on the mother and neonate. We compared the effects of intrathecal sufentanil 5 mcg and placebo when administered with hyperbaric bupivacaine 0.5% 11 mg for cesarean section.

Patients and Methods: Sixty parturients of ASA grading I and II of age between 18 to 45 years scheduled for elective cesarean section under subarachnoid block were randomly allocated into one of the two groups to receive 5µg sufentanil + 0.2ml sterile, preservative-free normal saline (Group S) and 0.3ml sterile, preservative-free normal saline (Group C) along with 2.2ml 0.5% hyperbaric bupivacaine making total volume to 2.5 ml.

Results: The two groups were compared with respect to their sensory and motor block characteristics, duration of analgesia, intraoperative haemodynamic changes, adverse effects and effect on neonatal Apgar score. Postoperative pain was assessed using the visual analog scale (VAS). Duration of analgesia was defined as the time taken for a VAS score of 4 to be achieved. Mean duration of analgesia was significantly prolonged in sufentanil group (184.0 ± 51.50 minutes) than the control group (107.0 ± 46.40 minutes). There is faster onset of sensory and motor block in the sufentanil group. The incidences of bradycardia and hypotensive episodes were similar in the two groups. There was no evidence of respiratory depression in any of the patients in any groups. Pruritus was observed in 6 (20.0%) patients in Group S which was statistically significant. There was no significant effect on Apgar score of the neonate.

Conclusion: Thus the addition of Sufentanil (5 mcg) intrathecally provides improved postoperative analgesia and haemodynamic stability with minimal side effects.

KEYWORDS: Cesarean section, spinal anaesthesia, bupivacaine, sufentanil.

Spinal anaesthesia has increasingly become the technique of choice for cesarean section due to its advantage of rapid onset of action, simplicity and reliability in producing uniform sensory and motor block. One disadvantage of spinal anaesthesia using local anaesthetic alone is a relatively short duration of action and hence lack of long-lasting postoperative analgesia. To overcome this problem, many adjuvants have been used to prolong the duration of analgesia. These include various opioids and non-opioid drugs. The rationale behind adding opioids to intrathecal local anaesthetics is that opioids act synergistically with local anaesthetics. Lipophilic opioid sufentanil added to intrathecal bupivacaine for cesarean section has shown to improve intraoperative and postoperative analgesia with no adverse effects on the mother and neonate. The aim of this study was to compare intrathecal hyperbaric Bupivacaine with Sufentanil and intrathecal hyperbaric Bupivacaine with placebo in parturients for cesarean section with respect to sensory and motor block characteristics, intraoperative Haemodynamic variables, postoperative analgesia and Apgar score of neonate at 1, 5 and 10 minutes.

MATERIAL AND METHODS

This study was performed in sixty female patients undergoing elective Cesarean section under subarachnoid block in a randomized prospective double blind comparative method after approval by the hospital ethics committee and written and informed consent of the patients. Patients with ASA grading I or II, age between 18 to 45 years, height between 155 cm to 170 cm were included in the study. Patients with complicated pregnancies such as multiple pregnancy, pregnancy induced hypertension (PIH), ASA grading III and IV and contraindication to spinal anesthesia were excluded from study.

All patients were kept fasting for six hours and were premedicated with tab. ramlidine 150 mg and tab. ranitidine metoclopramide orally 2 hrs before surgery. Intravenous accesses was secured using a 20G intravenous cannula on the dorsum of the non-dominant hand and were pre loaded with lactated Ringers solution (10 ml kg⁻¹ body wt).
The local anaesthetic solution was prepared by one anaesthesiologist who didn’t take part in any further evaluation and monitoring, while another anaesthesiologist who was blinded to the group administered the anaesthetic and monitored the patient intraoperatively and postoperatively. In study group C, 2.5 ml of 2.2 ml (11mg) 0.5% heavy bupivacaine + 0.3ml sterile, preservative-free normal saline and in group S, 2.5 ml of 2.2 ml (11mg) 0.5% heavy bupivacaine + 5mcg (0.1ml) of Sufentanil + 0.2 ml of sterile, preservative-free normal saline was given intrathecally.

Subarachnoid block was carried out under all aseptic precautions, in the sitting position after giving local anaesthesia 2ml of 2% lignocaine using the midline approach with a 25G spinal needle in the L3-4 interspace and the respective solution injected after a free and clear flow of cerebrospinal fluid. The patients were then immediately made to lie supine with a wedge placed under right hip. All patients received 2 l/min oxygen by nasal cannula.

Heart rate, non invasive blood pressure, oxygen saturation, and respiratory rate were recorded using a multi-channel monitor every 2 minutes for the first 20 minutes and then every 5 minutes till end of surgery. For the purpose of the study, bradycardia was defined as a fall in heart rate below 20% of baseline values or a heart rate less than 60 beats/minute whichever was less. Any bradycardia was treated with Inj. Atropine 0.01mg kg⁻¹ body weight intravenously.

Hypotension was defined as a fall in systolic blood pressure by more than 25% of baseline values or an absolute fall in blood pressure below 90 mm Hg. Any hypotension was treated with fluid boluses of 50-100ml, or Inj. Ephedrine in aliquots of 5 mg intravenously.

Respiratory depression was defined as a fall in respiratory rate below 10 breaths per minute and would have been treated with Inj. Naloxone (1-2 mcg kg⁻¹) IV.

Sensory block was assessed every 2 minutes till 20 minutes, by pin-prick using a sterile 20G hypodermic needle, in the midline. Onset of sensory block was defined as the achievement of sensory level of L1. The highest sensory level and the time taken to achieve it were recorded. The time taken for the sensory block to regress to T10 was recorded. Duration of sensory block was recorded as the time taken for the sensory level to regress to S1.

Motor block was assessed every 2 minute till 20 minutes using the Bromage scale. Onset of motor block was defined as the achievement of Bromage I and complete motor block as Bromage III. The duration of motor block was defined as the time taken for complete regression of the motor block to Bromage 0.

The patients were monitored for adverse effects viz. respiratory depression, nausea and vomiting, and pruritus. Pruritus was treated with Inj. Chlorpheniramine 10mg IV, Nausea and vomiting with Inj. Ondansetron 4 mg. IV.

Postoperatively sensory and motor blocks were assessed every 30 minutes till 4 hours after surgery and pain was assessed using Visual Analog Scale (VAS). Visual Analog Scale (VAS) of 1 to 10 was shown preoperatively to the patient and the procedure of postoperative pain measurement was explained in detail, with 0 corresponding to no pain and 10 to the worst pain imaginable. Duration of analgesia was defined as the time taken for a VAS score of 4 to be achieved at which point the patients were administered rescue analgesia in the form of inj. Diclofenac 75 mg diluted in 10 ml distilled water given intravenously over 5 minutes. Any adverse effects were noted and treated appropriately.

Statistical tests were performed and results are reported as absolute values or mean + SD where appropriate. Data were compared using Unpaired t-test and Mann-Whitney test. A “p” value of <0.05 was considered significant.

RESULTS

There was no significant difference with respect to the age, height and weight distribution and ASA grading.

The mean duration of surgery in sufentanil group was 60.50 ± 12.82 minutes and 70.03 ± 13.55 minutes in the control group. The difference is statistically significant as 'p' value is 0.007 which is <0.05. The duration of surgery in sufentanil group is much less as compared to control group. This may be attributed to the fact that sufentanil caused faster onset of action of sensory and motor block, hence surgery was started early and due to the shorter duration of surgery.

Table 1

| Variables | Sufentanil Group | Control Group | Unpaired t-test applied |
|-----------|----------------|--------------|------------------------|
|           | No. | Mean | SD | No. | Mean | SD | t-value | p-value | Difference |
| Age (years) | 30 | 27.33 | 3.99 | 30 | 27.13 | 4.30 | 0.187 | 0.852 | Not significant |
| Height (cm) | 30 | 160.47 | 4.64 | 30 | 158.77 | 4.25 | 1.479 | 0.144 | Not significant |
| Weight (kg) | 30 | 58.83 | 10.16 | 30 | 61.20 | 8.51 | -0.978 | 0.332 | Not significant |
to better relaxation could end the surgery much earlier than the control group.

There was statistically significant difference in the motor and sensory block characteristics with the onset, duration, and time to maximum block between the two groups as the p value is < 0.05. There was faster onset of block in the sufentanil group. There were statistically significant difference in the time required to reach the highest sensory level between the two groups. Time to achieve highest sensory level was 10.67 ± 2.19 minutes in sufentanil group and 13.33 ± 2.19 minutes in the control group. The difference being significant statistically.

The duration of analgesia was prolonged in Groups S as compared to Group C. Mean duration of analgesia in sufentanil group was 184.0 ± 51.50 minutes and 107.0 ± 46.40 minutes in the control group. This was statistically significant.

The differences in the baseline pulse rates between the two groups were not statistically significant. There was a slowing of the heart rate among both the groups till approximately 14 minutes after giving spinal anaesthesia.

Table 2
Duration of surgery in the two groups

| Variables        | No. | Sufentanil | Control | Unpaired t-test applied |
|------------------|-----|------------|---------|-------------------------|
| Duration of      |     |            |         |                         |
| Surgery (min)    | 30  | 60.50      | 12.82   |                         |
|                  | 30  | 70.03      | 13.55   | -2.800                  |
|                  |     |            |         | 0.007                   |
|                  |     |            |         | Significant             |

9.90E-08 = 9.90 x 10^-8

Table 3
Duration of analgesia

| Variables        | No. | Sufentanil | Control | Unpaired t-test applied |
|------------------|-----|------------|---------|-------------------------|
| Duration of      |     |            |         |                         |
| Analgesia (min)  | 30  | 184.00     | 51.50   |                         |
|                  | 30  | 107.00     | 46.40   |                         |
|                  |     |            |         | 6.084                   |
|                  |     |            |         | 9.90E-08                |
|                  |     |            |         | Significant             |

Table 4
Adverse effects

| Adverse effects | Group Sufentanil | Group Control | Total | Chi-square test | P value |
|-----------------|------------------|---------------|-------|-----------------|---------|
| Pruritus ^      | No. 6            | 0             | 6     | 4.630           | 0.0314  |
| % 20.0%         | 0.0%             | 10.0%         |       |                 |         |
| Nausea ^        | No. 4            | 5             | 43    | 0.873           | 0.3502  |
| % 33.3%         | 13.3%            | 8.3%          |       |                 |         |
| Vomiting ^      | No. 4            | 4             | 45    | 2.411           | 0.1205  |
| % 0.0%          | 13.3%            | 6.7%          |       |                 |         |
| None            | No. 23           | 22            | 45    | 0.000           | 1.000   |
| % 77.7%         | 73.3%            | 75.0%         |       |                 |         |
| Total           | No. 30           | 30            | 60    |                 |         |
| % 100.0%        | 100.0%           | 100.0%        |       |                 |         |

Figure 1
A comprehensive and statistical analysis of duration of surgery, duration of analgesia, duration of sensory and motor block in the two groups

Only 2 patients in sufentanil group developed bradycardia. Hence the incidence of bradycardia was not statistically significant. Regarding blood pressure no statistically
significant difference was seen in the two groups at most of the time. A fall in the blood pressures was observed in both the groups after administration of subarachnoid block. However, the incidence of hypotension in the two groups was similar and not statistically significant. No patient had a respiratory rate less than 10 breaths per minute. All the patients in both the groups maintained SpO2 above 98% during the surgery.

VAS was statistically significant till 150 minutes post operatively. It was significantly low in the sufentanil group than the control group. Rescue analgesia was administered when a VAS of 4 was achieved by the patient. In control group rescue analgesia was required approximately after 150 minutes and after 240 minutes in sufentanil group.

DISCUSSION
In our study we found that the addition of 5 mcg of Sufentanil to 11mg of Bupivacaine (0.5% 2.2ml) administered intrathecally significantly prolonged the duration of analgesia. This provided improved patient comfort and reduced the need for intramuscular and intravenous analgesia in the immediate postoperative period. Opioids when added to local anaesthetics act synergistically and improve the quality of subarachnoid block and provide prolonged postoperative analgesia.

The mean duration of analgesia in our study was 184.0±51.50 minutes in Group S and 107.0±46.40 minutes in Group C. Application of the Unpaired t-test resulted in "p" value of 9.90E-08 which is statistically significant. Vandana Trivedi and Amit Jha\textsuperscript{1} observed that the duration of analgesia was 195 ± 19.39 minutes in fentanyl group and 305 ± 48.95 minutes in sufentanil group. Thus an increase of 156% in the mean duration of complete analgesia was noted in sufentanil group. Dahlgren et al\textsuperscript{2} showed that the addition of opioids improved the quality of subarachnoid block including the duration of analgesia in the early postoperative period as compared with the placebo, with sufentanil having a longer duration of action than fentanyl. Nelson et al\textsuperscript{3} compared intrathecal fentanyl and sufentanil for labor analgesia and estimated that intrathecal sufentanil is approximately 4.5 times more potent than fentanyl. Hence, we used sufentanil in a dose of 5µg.

The µ agonist sufentanil acts by decreasing the conductance of voltage gated calcium channels or by opening the inward flowing potassium channels. Either of these effects results in decreased neuronal activity. It also has a post-synaptic effect resulting in hyperpolarisation and reduction in neuronal activity. The local anaesthetic, bupivacaine, acts by blocking the voltage gated sodium channels. These effects may contribute to the synergism observed between local anaesthetics and opioids\textsuperscript{4}. Onset of sensory and motor block was early in sufentanil group as compared to control group. In this study, the mean time to onset of sensory block was 0.13±0.51 minutes (mean ± SD) in Group S and 1.13±1.63 minutes in Group C. The mean time to the achievement of the highest sensory level was 10.67±2.19 minutes in Group S and 13.33±2.19 minutes in Group C. By applying the unpaired t-test, we get a "p" value of 0.0 for the onset of sensory block and 0.0 for the time to achieve the highest sensory level. All of these were statistically significant. The faster rostral spread is attributed to increased lipophilicity of sufentanil. Amit agarwal et al\textsuperscript{5} observed mean time to achieve highest sensory level was 4.64 ± 0.28 minutes in bupivacaine group, 4.30 ± 0.12 minutes in fentanyl group and 1.92 ± 0.27 minutes in sufentanil group. Hence time to achieve the maximum height was significantly faster with use of sufentanil (p<.05). Thus observations of our study are nearly similar to this study.

In our study we found that sensory block was much more prolonged in sufentanil group. The duration of the sensory block in Group S was 120±35.23 minutes and in Group C was 84.0±41.99 minutes. Applying the Unpaired t-test, the "p" value was calculated to be 0.0 which was significant statistically. Our finding were similar to the study by Dahlgren et al\textsuperscript{2} who observed that the mean regression time for sensory level was 130.5±20.7 minutes in the placebo group.
148.4±29.5 minutes in the fentanyl group, 165.8 ± 40.1 in 2.5 mcg sufentanil group and 161.8±27.6 minutes in the 5 mcg sufentanil group. They found that the time to regression of the sensory level to T10 was significantly delayed in the sufentanil group as compared to the placebo group.

There were no statistically significant differences in the intraoperative haemodynamic parameters in the two groups. After administration of spinal anaesthesia, a fall in the heart rate was observed in both the two groups. 2 patients (20%) in Group S and 0 in Group C (0%) had episodes of bradycardia. By the application of Pearson Chi-Square test this was not found to be statistically significant as "p" value was 0.4720. The blockade of the afferent sympathetic fibres from T1 - T4 can cause a loss of chronotropic drive resulting in bradycardia. At the same time opioids also cause bradycardia by blocking the preganglionic sympathetic nerves causing a reduction in the preganglionic sympathetic activity and bradycardia. The incidences of hypotensive episodes were similar in the two groups. There was no evidence of respiratory depression in any of the patients in any groups.

Regarding adverse effects no statistically significant difference was seen in incidence of nausea and vomiting. It was however observed that the incidence of nausea was lower in the groups receiving opioids. Hence anti-emetics were needed only in placebo group and this is consistent with the study by Dahlgren et al who reported that anti-emetics were required only in the placebo group and no patients in the groups receiving intrathecal opioids required any pharmacological intervention.

Pruritus was seen exclusively in the group that received sufentanil. 6 patients (20.0%) in Group S developed pruritus which was statistically significant. Pruritus was elicited only after direct questioning and only 1 patient required treatment which was not significant. The study conducted by A. de F. de Assuncao Braga et al concluded that addition of 7.5 mcg of sufentanil to hyperbaric bupivacaine provided adequate anesthesia and good postoperative analgesia. Pruritus was the most common side-effect and had a higher incidence with 7.5 mcg sufentanil. Ngiam et al showed higher incidence of pruritus (35%) in sufentanil group, probably due to the higher dose (15 mcg sufentanil) used which justifies the dose used in our study i.e. 5 mcg sufentanil.

In our study we found no statistical significant difference in the apgar score at 1, 5 and 10 minutes of the neonate which was in accordance with the study done by Amit agarwal et al who observed that the neonatal outcome as judged by Apgar score at 1, 5 & 10 mins were similar in all the groups. Thus the addition of opioid intrathecally was not found to be associated with any significant fetal depression. Thus from the above study it can be concluded that the addition of sufentanil to local anaesthetics prolongs the duration of subarachnoid block and the duration of analgesia in the early postoperative period. Few adverse effects may occur which are mild and can be easily treated.

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