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Intrathecal Hyperbaric Bupivacaine With Fentanyl or Clonidine in Caesarean Section and Post Caesarean Analgesia – A Randomised Double Blind Controlled Trial.

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ABSTRACT

Background: Spinal anaesthesia has become the method of choice for caesarean section and hyperbaric bupivacaine is the most commonly used drug. Intrathecal fentanyl is reported to augment analgesia produced by local anaesthetics through binding with spinal opioid receptors. Clonidine has antinociceptive effect by its action on the spinal α2 receptors and intrathecal clonidine has been successfully used for postcaesarean analgesia. Objectives: To compare efficacy and side effects of fentanyl and clonidine as adjuvant to hyperbaric bupivacaine used in spinal anaesthesia for caesarean section. **Methods:** Ninety healthy patients of ASA physical status I & II, aged 18-30 years, undergoing elective caesarean section under spinal anaesthesia were randomized to two equal groups. One received 25 µg fentanyl and another 45 µg clonidine, with 0.5% hyperbaric bupivacaine (2.2 ml) intrathecally in total volume of 2.8 ml made up by addition of normal saline. Heart rate, blood pressure and SpO2 were documented at regular intervals. Pain scores were recorded by visual analogue scale. **Results:** The duration of analgesia was 236.9 ± 19.70 min with fentanyl and 217.2 ± 20.32 min with clonidine ($p < 0.001$). Hypotension occurred in 19 and 37 subjects receiving fentanyl and clonidine respectively ($p < 0.001$). **Conclusion:** Clonidine is not superior to fentanyl intrathecally as hypotension is more frequent without any significant prolongation of analgesia.

Keywords: Bupivacaine, clonidine, caesarean section, fentanyl, Spinal anaesthesia.

INTRODUCTION

Spinal anaesthesia provides faster onset and superior block in caesarean section.[1] Hyperbaric bupivacaine is the most commonly used drug. Various adjuvants, are used with bupivacaine for prolongation of subarachnoid block.[2,3] Fentanyl, a highly lipid soluble, a potent opioid receptor agonist has been largely used with various local anesthetics for a wide variety of surgical procedures.[4,5] Opioids such as morphine, fentanyl, and sufentanil have been used as adjuncts in spinal anaesthesia to increase the duration of postoperative analgesia. Although they ensure superior quality of analgesia, they are associated with many side effects such as pruritis, nausea, vomiting, urinary retention, and especially late and unpredictable respiratory depression.[6] Intrathecal clonidine has a substantial antinociceptive effect by its action on the α2-receptor in the dorsal horn of the spinal cord.[7,8] Clonidine administered intrathecally also produces dose-dependent analgesia and it has been used successfully as a sole analgesic for pain relief in labour and for postoperative pain management after Caesarean section.[9,10] Intrathecally both fentanyl and clonidine if used in low doses with hyperbaric bupivacaine are safe and prolong postoperative analgesia. Thorough literature search revealed paucity of studies directly comparing these two drugs for their efficacy and safety. Present study was designed to directly compare these two drugs. With this preview the study was conducted to compare efficacy and side effects of fentanyl and clonidine as adjuvant to hyperbaric bupivacaine used in spinal anaesthesia for caesarean section

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MATERIALS AND METHODS

After the approval of the Institutional Ethics Committee and written informed consent from each patient the study was carried out under the Department of Anaesthesiology, Burdwan Medial College & Hospital, Burdwan between April 2011 to March 2012. 90 healthy women of ASA grade I and

II, aged 18 – 30 yrs scheduled for elective caesarean section participated in the study. Patients with complicated pregnancy including pregnancy induced hypertension, placenta praevia, abruption placentae, severe systemic disorders like diabetes mellitus, hypertension, heart disease changing ASA grade to more than II, allergy to bupivacaine, fentanyl or clonidine and all known contraindications for spinal anaesthesia, such as spine deformity, increased intracranial pressure, neurological disorders, haemorrhagic diathesis, or infection at the puncture site were excluded from the study.

Patients were randomly distributed according to a computer-generated random number list into two groups of 45 patients each. Preoperative evaluation done and all women were received Tab. Ranitidine (150mg) and Tab. Metoclopramide (10mg) 1 hour before termination. Before induction of spinal anaesthesia patients were preloaded with intravenous infusion of Ringer's lactate solution 20ml/kg body weight through 18 G intra venous cannula. Hemodynamic monitoring consisted of a five-lead electrocardiogram, non invasive blood pressure and peripheral oxygen saturation were done. All baseline parameters were recorded. Subarachnoid block was established with 27G spinal needle in lateral position through midline approach between L2-L3 or L3-L4 vertebral space. After clear CSF flow was observed patients in Group A received 25 µg fentanyl and patients in Group B 45 µg clonidine, with 0.5% hyperbaric bupivacaine (2.2ml) intrathecally in total volume of 2.8 ml by addition of normal saline. The type of study drug used was unknown to anaesthesiologist administering the anaesthesia or to the anaesthesiologist who evaluated patient's responses.

Immediately after the intrathecal injection, patients were placed in the supine position and left uterine displacement was maintained by placing the wedge under the right hip. Oxygen (4L/min) by facemask was given until delivery. Surgery was started when sensorial block reached T4 level. Apgar score was recorded at 1 min & 5 min after birth. No analgesia and sedation was given. Postoperative analgesia was evaluated by determining the time interval between subarachnoid block and the first rescue analgesia.

The following parameters were noted

- Duration of sensory block - assessed every 15 minutes postoperatively by pin prick method. Time duration (minute) was assessed from onset of sensory block to regression of dermatome of two segments.
- Duration of analgesia - assessed every 15 minutes postoperatively by 10 cm Visual Analogue Scale (VAS). Time duration (minute) was assessed from onset of sensory block to first request for rescue analgesic or VAS score 4 or more. The numeric pain scale was of 0-10 cm (0 = no pain and 10 = worst possible pain). Rescue analgesic injection Diclofenac sodium 1.5mg/kg was given intramuscularly.
- Hemodynamic parameters - pulse, blood pressure (mean), were recorded at 0 minute, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes, 60 minutes after administration of subarachnoid block.
- Foetal wellbeing – was assessed in both groups by APGAR scores at one minute and five minutes after birth.
- Side effects - nausea, vomiting, pruritus, respiratory depression, shivering etc were noted. Urinary retention was not assessed as every patient had a urethral catheter in situ for 24 hours.

All measurements and assessments were recorded by an anaesthesiologist who was unaware of the medication.

Statistical Analysis

Duration of analgesia was considered as the primary variable and sample size was calculated on it. On the basis of previous study average duration in each group was 200 min and to detect a difference of 10% (i.e. 20 min), at the $P<0.05$ level with a probability of detecting a difference of 80 percent (1−beta=0.80). Assuming that within group SD was 20 min and we needed to study at least 45 patients per group to be able to reject the null hypothesis. Raw data were entered into an MS Excel spreadsheet and analysed using standard statistical software. Categorical variables were analysed using the Pearson's Chi square test or Fisher's Exact Test, which one is applicable. Normally distributed continuous variables were analysed using the independent sample t test and P value <0.05 was considered statistically significant.

RESULTS

Both groups were comparable in respect to their demographic profile [Table 1]. There was no significant difference in them regarding age, body weight, height and duration of surgery ($p>0.05$).

Table 1: Distribution of age, body weight and height of patients and duration of surgery (min) in both groups.

	Group-A (n=45)	Group-B (n=45)	p Value
Age(year)	23.42±2.86	23.93±2.85	0.807
Body wt.(kg)	49.47±6.15	47.49±7.56	0.512
Height(cm)	144.67±7.6	145.64±7.2	0.578
Duration of surgery(min)	37.62±4.10	36.02±5.47	0.139

In present study the duration of sensory block in the two groups was calculated by counting time required to two segment regression of sensory block after surgery under spinal anaesthesia. There was statistically significant difference (p=0.000) among the Group-A and Group-B in respect to the duration of sensory block shown in the [Table 2]. Duration of analgesia was assessed every 15 minutes

postoperatively by 10 cm Visual Analogue Scale (VAS). There was statistically significant difference (p=0.000) between the Group-A and Group-B in respect to the duration of analgesia. This was assessed on the basis of VAS score in the post-operative period (When VAS score≥4) or patient demand for analgesics in the post-operative period. Thus duration of analgesia was longer in Group-A (236.87±19.703min) as compared to Group-B (217.22±20.326min).

Table 2: Distribution of duration of sensory block (two segment regression) and duration of analgesia between two groups

	Group A (n=45)	Group B (n=45)	p value
Two Segment Regression time (min)	185.76±17.974	145.84±15.368	0.000
Duration of Analgesia (min)	236.87±19.703	217.22±20.326	0.000

[Table 3] shows overall foetal wellbeing in both groups. APGAR scores at one minute and 5 minutes after birth were comparable in both groups. (p>0.05)

Table 3: Distribution of apgar score between two groups.

Time	Group A (n=45)	Group B (n=45)	p value
1 min	9.04±0.10	8.64±1.10	0.0730
5min	9.48±0.42	9.73±0.49	0.2561400

Incidence of hypotension was more frequent in Group B (82.22%) than Group A (42.22%) which was statistically significant (p<0.001). Other complications were infrequent.

Table 4 Comparison between group-A and group-B according to the incidence of side-effects.

	Group-A	Group-B	Significance
Bradycardia	1(2.22%)	1(2.22%)	P=1.000
Hypotension	19(42.22%)	37(82.22%)	P=0.0002
Nausea& Vomiting	6 (13.33%)	8(17.78%)	P=0.7722
Pruritus	1 (2.22%)	0(0%)	P=1.000
Respiratory Depression	0 (0%)	0 (0%)	P=1.000
Sedation	0 (0%)	0 (0%)	P=1.000

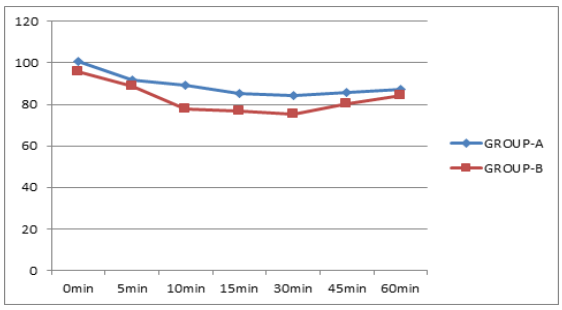

Figure 1: Distribution of mean arterial blood pressure that changes during study period between two groups.

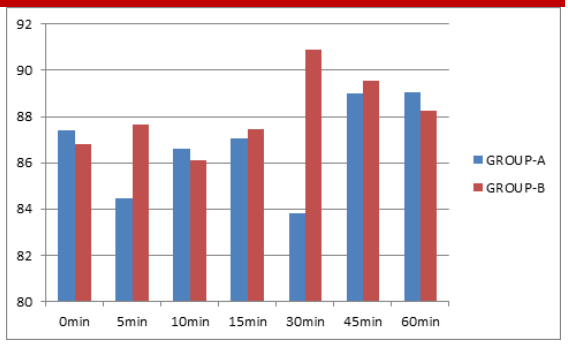

Figure 2: Distribution Of Changes In Heart Rate Between Two Groups During Study Period.

DISCUSSION

The addition of opioid to local anaesthetic in management of subarachnoid block is widely accepted practice in anaesthesiology. Fentanyl citrate, a μ-1 and μ-2 agonist is a very potent drug because of its high lipophilicity. It is preferred as an adjuvant in spinal anaesthesia because of its rapid onset and short duration of action with lesser incidence of respiratory depression.[11] However pruritus, nausea, vomiting, activation of herpes labialis, urinary retention and late and especially unpredictable, respiratory depression of other opioids have directed pain research towards non-opioids6. Analgesic properties of clonidine have been shown to depend on the activation of α2 receptors located in the dorsal horn. Presynaptic stimulation of α2 receptors inhibits neurotransmitter release and postsynaptic stimulation prevents neuronal transmission through hyperpolarisation.[12] Although prolongation of the effects of local anesthetics has been reported for oral and intravenous clonidine, the intrathecal route is more effective; clonidine prolongs the duration of action of intrathecal administered local anesthetics and has potent antinociceptive properties.[13] The addition of clonidine is better than the opiods when side effects on the maternal physiology as well as the fetal Apgar scores are considered.[14]

To compare the efficacy we used the duration of effective analgesia measured by time in minutes for requirement of rescue analgesia. This was assessed on the basis of VAS score in the post-operative period (When VAS score≥4) or patient demand for analgesics in the post-operative period. We observed that there was significant difference (p=0.000) among the Group-A and Group-B in respect to the duration of analgesia, duration of analgesia was longer in Group-A (236.87 min) as compared to Group-B (217.22 min). In consistency to results of several other studies we found both drugs to be effective as adjuvants to intrathecal bupivacaine prolonging the duration of analgesia.[11,14-17] Benhamou and colleagues studied 78 women scheduled for Caesarean section comparing the intraoperative analgesic effect and the time to first

analgesic request of the addition of 75 mg clonidine or 75 mg clonidine plus fentanyl to hyperbaric bupivacaine.[11] This study also showed that addition of clonidine prolonged the postoperative analgesia. In present study the duration of sensory block in the two groups was calculated by counting time required to two segment regression of sensory block after surgery under spinal anaesthesia. Duration of sensory block was prolonged in Group-A (185.76±17.974 min) patients than in Group-B (145.84±15.368) patients. There was statistically significant difference (p=0.000) among the Group-A and Group-B in respect to the duration of sensory block.

In our study we found only two patients had bradycardia which got corrected on its own. We observed no difference in comparing incidence of bradycardia between two groups. In our study we found incidence of hypotension significantly more in patients received clonidine (82.22%) than in patients received fentanyl (42.22%) which was different to other studies.[15] Kothari N et al found the incidence of both hypotension and bradycardia more in bupivacaine group than in bupivacaine with clonidine group.[15] Bajwa SJ who used 9mg of bupivacaine also did not observe bradycardia by addition of clonidine even up to 45µg.[14] Shah BB and Sethi BS who used 1µg /kg of intrathecal clonidine for non-obstetric surgeries had also very few incidences of hypotension and bradycardia requiring intervention.[18,19] Biswas et al and Agrawal A et al observed similar haemodynamic stability with 12.5µg and 25µg of intrathecal fentanyl.[16,17]

Studies showed that addition of fentanyl increased the incidence of sedation and pruritus.[11] We found that the incidence of pruritus was lower in the Bupivacaine with clonidine group compared with the Bupivacaine with fentanyl group (0% and 2.22%, respectively) but there was no statistically significant difference. In our study we observed no difference in sedation scores in between two groups. Kothari N et al also found 35 to 45% of patients drowsy by addition of 50µg of clonidine to bupivacaine;[15] but Bajwa SJ et al did not find any sedation by addition of up to 45µg of clonidine to bupivacaine which was similar to our finding.[14] Thus the sedation with clonidine is dose dependent. In our study we could not observe sedation with intrathecal fentanyl added to bupivacaine similar to Biswas BN et al,[16] Dahlgren G et al and Hunt CO et al.[20,21]

CONCLUSION

Both fentanyl and clonidine if used in low doses with hyperbaric bupivacaine are safe and prolong postoperative analgesia for patients undergoing caesarean section under spinal anaesthesia. Intrathecal addition of 25µg of fentanyl to bupivacaine gives longer duration of postoperative analgesia than 45µg clonidine, moreover incidence of hypotension is more with clonidine. In conclusion, Clonidine is not superior to fentanyl intrathecally as hypotension is more frequent without any significant prolongation of analgesia.

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