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ORIGINAL ARTICLE

COMPARATIVE EVALUATION OF INTRATHECAL BUPIVACAINE-FENTANYL AND BUPIVACAINE - CLONIDINE FOR CAESAREAN SECTION IN PREGNANCY INDUCED HYPERTENSION

Tripti Vatsalya[1], Vikas Kumar Gupta[2], Shikha Mehrotra[3]

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ABSTRACT: BACKGROUND: Pain free postoperative period and early ambulation are the need of the day for mothers and their neonates for early initiation of breast feeding. It is moral responsibility of Anaesthesiologist to provide a safe and pain free postoperative period with use of various techniques and drug combinations. Spinal anaesthesia has been widely used for caesarean section in normalas well as preeclamptic parturients and has been found to be efficaciousand safe. The present study aimed to compare the analgesic efficacy and side effect profile of intrathecal Bupivacaine with Fentanyl and Bupivacaine with Clonidine in cesarean section of parturients with pregnancy induced hypertension (PIH). **METHODS:** 50 full term parturients with pregnancy induced hypertension scheduled for cesarean section were randomized into 2 groups of 25 each. GROUP BF (Bupivacaine with Fentanyl) received 7.5mg of 0.5% hyperbaric Bupivacaine and 20µg Fentanyl intrathecally. GROUP BC (Bupivacaine with Clonidine) received 7.5mg of 0.5% hyperbaric Bupivacaine and 60µg clonidine intrathecally. **RESULTS:** Patients in group BC showed long lasting analgesia compared to group BF (p value<0.05). Both the groups had satisfactory analgesia with hemodynamic stability, however the incidence of hypotension and vasopressor requirement was more in group BC compared to BF. Incidence of pruritus was exceptionally seen in group BF, however more patients were sedated and complained of dry mouth in group BC. Both the groups had comparable APGAR scores with no adverse neonatal effects. **CONCLUSION:** We conclude use of intrathecal clonidine 60µg and Fentanyl 20µg both provide excellent sensory and motor blockage with lower dose of bupivacaine. Both drugs improved intraoperative analgesia and prolonged the duration of effective analgesia without any adverse effect on neonate neurobehaviour. Fairly good analgesia with less sedation and better haemodynamic stability is observed with 20µg fentanyl .Addition of 60µg of clonidine which gives excellent analgesia of significantly prolonged duration than fentanyl; along with sedation is also a better alternative for preeclamptic parturients undergoing cesarean section.

KEYWORDS: Pregnancy induced hypertension, Bupivacaine, Fentanyl, clonidine Spinal anaesthesia, cesarean section.

INTRODUCTION: Preeclampsia is a hypertensive disorder of gestation, complicating 5% to 7% of all pregnancies. It is characterized by new onset of hypertension (≥140/90 mmHg) and proteinuria that develops after 20 weeks of gestation and usually resolves within 48 h of fetal delivery. The administration of general anesthesia in such high risk parturients may cause exaggerated cardiovascular response to intubation leading to cerebral hemorrhage and pulmonary edema; thereby increasing morbidity and mortality in both mother and child.[1] Similarly, an exaggerated pressor response to intubation may increase the maternal plasma catecholamine concentration,

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which in turn impairs the uteroplacental blood flow,[2] Administration of regional anesthesia besides avoiding maternal complications with general anesthesia, improves uteroplacental blood flow and neonatal outcome. Spinal anesthesia offers rapid onset, more reliable anesthetic with low local anesthetic requirement, however it is essential to rule out underlying coagulopathy or a significant drop in the trend of platelet count prior to performing neuraxial techniques.

The addition of adjuvants prolongs the spinal anesthetic duration in addition to increased post-operative analgesic duration. Fentanyl is one of the most extensively used opioids for this purpose and has been found to be safe and effective both in terms of neonatal and maternal outcome, not only in normal parturients but also in severely preeclamptic patients, for labor analgesia and elective caesarean section,[3] but it is associated with many side effects such as pruritus, nausea, vomiting, urinary retention, and respiratory depression.[4] This directed the use of newer and better adjuvants to local anesthetic for spinal anesthesia such as Neostigmine, Ketamine, Midazolam, and Clonidine. [5]

Clonidine, a α2 adrenergic agonist like lipophilic opioids, can achieve analgesia from systemic, epidural, or intrathecal administration. Adding Clonidine to intrathecal Bupivacaine provides effective, prolonged, and dose dependent analgesia with a consequently decreased requirement for supplemental analgesics. [6]

Achieving a good hemodynamic stability and high quality perioperative anesthesia of consistently prolonged duration is an attractive goal, provided the drugs used has an acceptable side effect profile. Good postoperative analgesia is an important avenue to attenuate the surgical stress response.

METHODS: A randomized comparative study was carried out on 50 healthy full term parturients with pregnancy induced hypertension of ASA grade I and II, undergoing elective and emergency caesarean section after obtaining clearance from the institutional ethics committee. Pregnancy induced hypertension was defined as blood pressure between 140 –160 / 90 – 110 mm Hg with or without proteinuria.

EXCLUSION: Parturients with medical disorder, infection at the site of injection, coagulopathy and other bleeding diathesis, HELLP syndrome, cardiovascular disease, patients with fetal compromise, any respiratory disease, preexisting neurological deficit, seizures were excluded from the study.

After a detailed pre‐anesthetic check‐up and investigation, a written informed consent was obtained from patient. The antepartum management included seizure prophylaxis in patients with severe preeclampsia with magnesium sulfate (MgSo4) administered as a loading dose of 4g intravenously, followed by 1g hourly intravenously. On arrival in the operating room, standard anesthesia monitors were attached, which included pulse oximetry, electrocardiogram, and non‐invasive blood pressure and the baseline readings were recorded. All patients were administered 10ml/Kg of Ringer Lactate and received injection Ranitidine 50mg and injection Ondansetron 4mg intravenously before induction of spinal anesthesia. Patients were placed in left lateral position and under all aseptic precautions; lumbar puncture was performed with 25 gauge Quincke's spinal needle at L3-L4 intervertebral space. After confirmation of free flow of CSF patients were randomly allocated to either of the two groups to receive either 7.5 mg (1.5 ml) of 0.5% hyperbaric Bupivacaine with

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20µg (0.4ml) Fentanyl (GROUP BF) or 7.5mg (1.5ml) of 0.5% hyperbaric Bupivacaine with 60µg (0.4ml) Clonidine (GROUP BC) intrathecally.

The needle was then withdrawn and the patient was immediately placed in the wedged supine position. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and peripheral oxygen saturation was monitored and recorded throughout the surgery at every 3 min till the delivery of baby and every 5 min thereafter until the end of procedure. Urine output was also monitored. Supplemental oxygen at the rate of 4L/min was given through a facemask during the operation. Sensory block was tested by pinprick till the block reached T6 level and then the surgical incision was allowed. Motor block was evaluated using the Bromage scale.

Time from giving the subarachnoid block to the time when Bromage scale grade 4 was achieved was recorded as time of onset of motor block. The time taken from intrathecal injection to attainment of the highest level of sensory block was recorded. The time for sensory regression to T12 from highest sensory level and the duration of effective analgesia (time to request for the first dose of rescue analgesic by patients) was also noted. Duration of motor block was recorded from onset up to cessation of grade I block. Hypotension was defined as 20% decrease from baseline mean arterial pressure. It was treated with fluid bolus and with 6mg intravenous Ephedrine. Total Ephedrine requirements, number and duration of hypotension episodes were recorded. The Apgar score of the newborn was recorded at 1 min and at 5 min after birth. Side effects such as hypotension, bradycardia (heart rate <50 beats per minute), nausea, vomiting, dry mouth, pruritus and shivering were recorded Patients were assessed for degree of sedation and scoring was done with Campbell Sedation Score. The data was collected, assessed and statistically analyzed; Comparison of means was done using unpaired t test. For categorical data chi-square test was applied. P-value of < 0.05 was considered statistically significant.

RESULTS: Mean age of patients belonging to group BF and group BC were 23.68+1.9 and 23.84+1.9 years respectively. Similarly mean weight of patients in 2 groups were 61.1+3.2 and 62.7+3.5 Kg respectively. There was no statistically significant difference ($p>0.05$) in age and weight between the two groups. The duration of surgery was also similar.

The time to achieve T6 sensory level and onset of motor block was faster in fentanyl group as compared to clonidine group but the difference was not statistically significant($P>0.05$). The time to regress up to T_{12} and the duration of effective analgesia (172.76+8.90 min in group BF; 267.8+18.98 min in group BC) was significantly longer in clonidine group as compared to fentanyl group ($P<0.05$) The mean duration of motor block was also significantly prolonged in clonidine group as compared to fentanyl group (Table-1)

Time intervals	Group BF (N = 25) Mean + SD (In minutes)	Group BC (N = 25) Mean + SD (In minutes)
Time to T6 level	2.460 + 0.351	2.60 + 0.456
Highest sensory level	5.76 + 0.55	5.80 + 0.56
Time for regression to T12 dermatome	102.72 + 16.68	165.0+ 10.897
Duration of effective Analgesia	172.76 + 8.90	267.8 + 18.98
Onset of motor block	2.44 + 0.462	2.56 + 0.320
Total duration of motor block	128.4 + 17.720	176.2 + 11.20

Table 1: Characteristic of sensory and motor block

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There is no statistical difference in the mean pulse rate and respiratory rate between groups BF and BC at different time interval (P >0.05). None of the patients had respiratory depression (<10 breaths/min).The mean oxygen saturation measured at different time intervals were comparable between 2 groups. There is a moderate fall of blood pressure in both the groups (10 - 15 % drop from baseline) after 5 minute of spinal block which gradually returned to baseline with in an hour. However more patients in group BC required the treatment of hypotension (8%) than in group BF (4%). The incidence of hypotension in group BC was also significantly higher than in group BF. (Fig. - 1, 2, & 3)

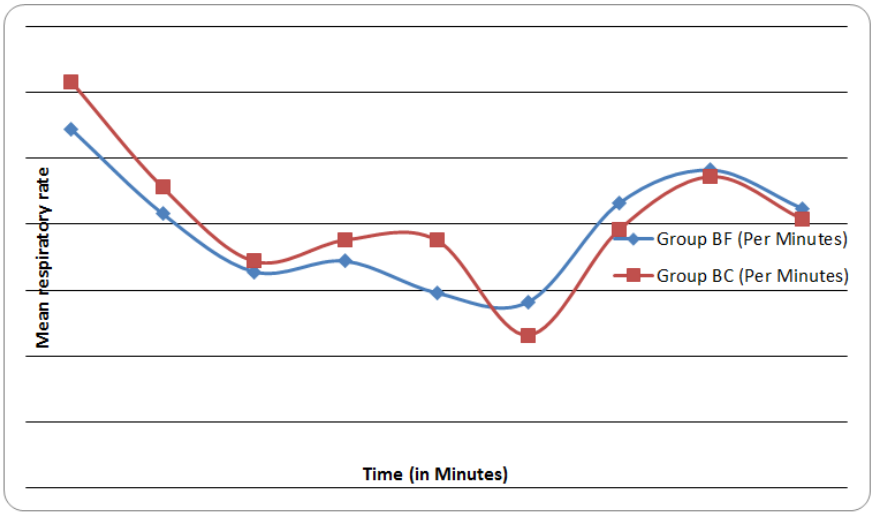

Fig. 1: Showing mean respiratory rate at different time intervals

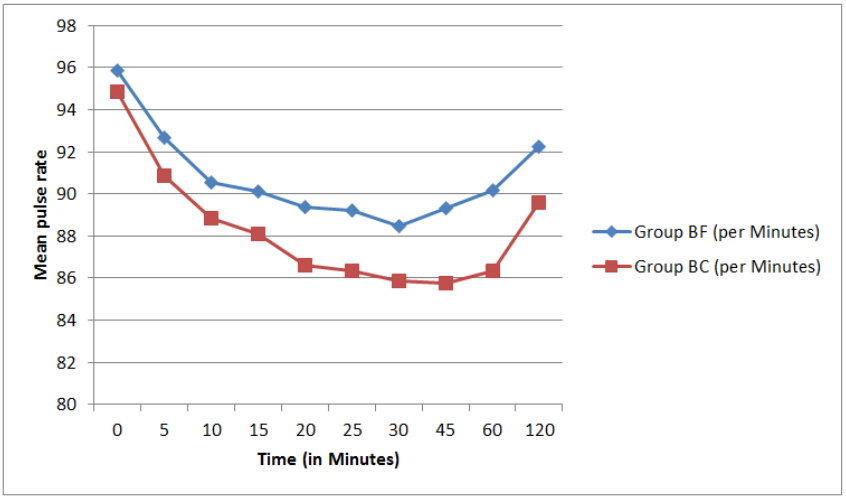

Fig. 2: Showing mean pulse rate at different time intervals

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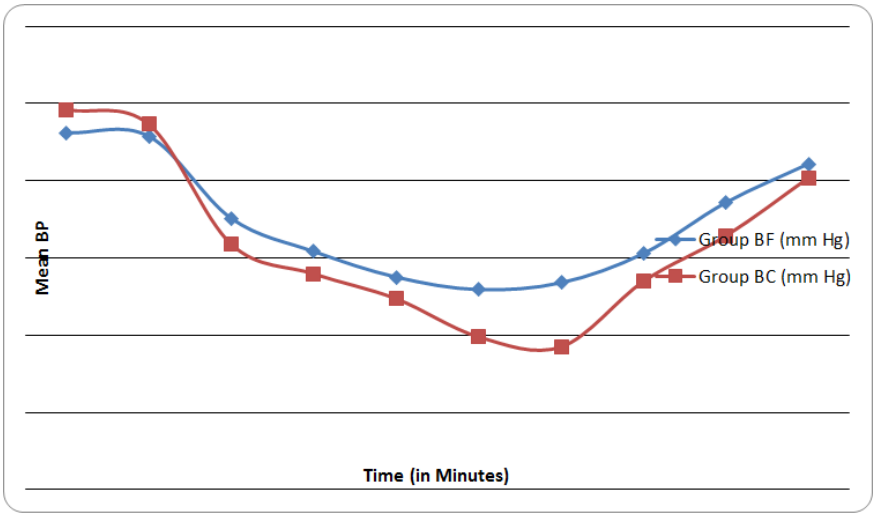

Fig. 3: Showing Mean Blood Pressure at different time intervals

Table 2 & 3 show Neonatal APGAR score and occurrence of complications in two groups respectively.

	1 min Mean + SD	5 min Mean + SD
Group – BF	9.16 + 0.374	10.00 + 0.00
Group – BC	9.08 + 0.276	10.00 + 0.00

Table 2: Neonatal Apgar score in two groups

Complications	Group BF (n = 25)		Group BC (n = 25)	
	No	%	No	%
Nausea/Vomiting	01	4%	3	12%
Pruritus	03	12%	0	0%
Shivering	02	8%	0	0%
Respiratory Depression	0	0%	0	0%
Hypotension	01	4%	02	8%
Bradycardia	01	4%	02	8%
Sedation	03	12%	18	72%

Table 3: Intra/postoperative complications

DISCUSSION: Efficacy and safety of spinal anesthesia with bupivacaine in preeclamptic parturients has been studied previously by various investigators. The incidence of spinal induced hypotension and the vasopressor requirement were found to be two times lower in preeclamptic parturients as compared to normal parturients undergoing Cesarean section and the increased sensitivity to

vasopressor drugs in preeclampsia along with the use of hyperbaric bupivacaine (8-12 mg) with opioids could decrease the spinal induced hypotension in pre-eclamptic parturient.[7]

Intrathecal administration of opioids with local anesthetics has potent synergistic analgesic effect, improves the quality of intraoperative analgesia with prolongation of postoperative analgesia.[8,9] An increased dose of fentanyl 0.5-0.75μg/kg intrathecally was associated with increased incidence of adverse effects in patients undergoing cesarean delivery [10]. So in present study 20μg fentanyl has been chosen to avoid the unacceptable effects. Similar dose of fentanyl has been studied previously by K Jain et al.[11]

Intrathecal Clonidine is being extensively evaluated as an alternative to neuraxial opioids for control of pain and has proven to be a potent analgesic, free of some of the opioid-related side effects.[12] A recent report established 1 μg/kg intrathecal clonidine as an adequate dose for prolonging bupivacaine spinal anesthesia in pregnant female.[13] Rochette et al. showed that clonidine at a dose of 1 μg/kg was not associated with hemodynamic disturbance.[14] So intrathecal doses of clonidine were titrated to 60 μg for pregnant females in our study in order to achieve adequate analgesia along with hemodynamic stability. Similar dose of clonidine has also been studied by Shah B B et al.[15]

In our study, the mean time of onset of sensory block at T6 and motor block is comparable in both the groups. Although it is little faster in clonidine group but the difference is not statistically significant.

Duration of effective analgesia was significantly prolonged in clonidine group as compared to fentanyl which is in line with the study of Singh et al.[16] Intrathecal clonidine increases the duration of both sensory block and motor block as well as postoperative pain relief. This finding is also consistent with the studies of Kothari N et al.[17] and Sethi B S.[13]

Addition of opioids to intrathecal Bupivacaine prolongs duration of analgesia evidence suggests that Bupivacaine increase the binding of morphine to opioids receptors, especially the highly dense kappa receptors, as the result of an associated conformational change in opioids receptors.[18] The mechanism of clonidine-induced potentiation of sensory block in spinal anesthesia is reported to be dependent on presynaptic decrease in transmitter release and postsynaptic increase in hyperpolarization.[19]

Parturients in both the group showed a significant fall in mean arterial pressure after 5-10min of spinal but MAP remained in the acceptable limit that is <20% of baseline. This stability may be attributed to low dose of bupivacaine used in our study. Also preloading the patient with 10ml/kg of ringer lactate and right side wedge placement may be the contributing factor.

Our findings regarding hemodynamic stability with use of Fentanyl are favored by studies of Sheikh F et al.[20] and Jain K et al.[11] Similarly the studies of Kothari N et al.[17] and Singh et al.[16] are in agreement with findings of hemodynamic stability in clonidine group. Also Shah B B[15] and Sethi B S[13] noticed very few incidence of hypotension and bradycardia requiring intervention with use of 1μg/kg of clonidine in non-obstetric surgeries.

In our study, we observed that there was fall in pulse rate after 10 minutes of intrathecal injection in clonidine and Fentanyl group. This was due to relief of anxiety because of sedative effect of Fentanyl and clonidine. However, fall was not more than 20%.Bradycardia was observed in 2 patients in clonidine group and 1 in fentanyl group out of these only 1 patient in clonidine group required i.v. Atropine 0.6mg.

Nausea and vomiting was observed more in Clonidine group. This result is in contrast to findings of Singh et.al,[16] who observed 45.5% higher incidence in Fentanyl group. This variation may be due to more incidence of hypotensive episodes and bradycardia in clonidine group. Also the doses of Bupivacaine and Fentanyl in our study are less than those of Singh et al.[16] Less nausea is seen in patient receiving mini-dose bupivacaine with fentanyl. It has been found that hypotension and excessive elevated blood pressure following administration of a vasopressor is the cause for nausea and vomiting during spinal anesthesia. Although dryness of mouth is a common side effect with clonidine but only 2 patients complained of this out of which one also received Atropine.

We observed more sedation scores in BC 60 group than in BF 20 group. In our study 72% patients in BC group were sedated in contrast to 12% in BF group, but none of these patients had respiratory depression. Kothari N et al.[17] also found 35 to 45% of patients drowsy with 50µg clonidine; but Bajwa S J et al.[21] did not find any sedation with 45µg of clonidine. This implies that the sedation with clonidine is dose dependent. Pruritus and shivering were found exclusively in fentanyl group. Urinary retention is more common after neuraxial opioid administration, could not be evaluated as all the patients of the study, routinely had a Foley's catheter for 24 hours.

None of the neonates in the study group had a 1min or 5min Apgar score less than 7.Neither fentanyl nor did clonidine have any deleterious effect on neonates in the study. Abbound et al. have found that preeclamptic patients have higher catecholamine concentrations than normal parturients. Elevated catecholamines along with decreased uterine blood flow in preeclamptics increases risk of further undesirable fetal effects. The sympathetic blockade that results from neuraxial anesthetic techniques have shown to improve intervillous blood flow in preeclamptic parturients by decreasing uteroplacental resistance. Also Fentanyl decreases circulating catecholamine levels in parturients due to pain relief.[22, 23] One of the limitations of this study was that umbilical pH and blood gas status could not be done for evaluation of fetal outcome.

CONCLUSION: We conclude use of intrathecal clonidine 60µg and Fentanyl 20µg both provide excellent sensory and motor blockage with lower dose of bupivacaine. Both the drugs improved intraoperative analgesia and prolonged the duration of effective analgesia without significant effect on neonate neurobehaviour. Fairly good analgesia with less sedation and better hemodynamic stability is observed with 20µg fentanyl. Addition of 60µg of clonidine which gives excellent analgesia of significantly prolonged duration than fentanyl; along with sedation is also a better alternative for preeclamptic parturients undergoing cesarean section.

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AUTHORS:

1. Tripti Vatsalya
2. Vikas Kumar Gupta
3. Shikha Mehrotra

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Anaesthesiology, Gandhi Medical College, Hamidia Hospital, Bhopal, M.P. India.
2. Assistant Professor, Department of Anaesthesiology, Gandhi Medical College, Hamidia Hospital, Bhopal, M.P. India.
3. Professor, Department of Anaesthesiology, Gandhi Medical College, Hamidia Hospital, Bhopal, M.P. India.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Tripti Vatsalya,
65 – Rishi Villas, Abbas Nagar Road,
Gandhi Nagar, Bhopal – 462036,
M. P, India.
Email: vbrtripti@gmail.com

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