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Research Article

COMPARE THE EFFECTS OF FENTANYL AND CLONIDINE AS ADJUVANT TO INTRATHECAL LEVOBUPIVACAINE IN PRE-ECLAMPSIA PATIENTS FOR CAESAREAN

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A B S T R A C T

Background- The pre-eclampsia patients may carry a high risk with use of spinal anesthesia owing to possibility of severe hypotension. Low dose of anaesthetic agent with adjuvant is safely use as a regional anesthesia in pre-eclampsia cases, and need of general anesthesia can be avoid, which is itself related to maternal and fetal complication.

Objective: To compare the effects of fentanyl and clonidine as adjunct to levobupivacaine, administered by intrathecal route in pre-eclampsia patients.

Methods: This was a prospective comparative study conducted on sixty pre-eclampsia parturient planned for emergency caesarean delivery under spinal anesthesia. Patients were divided into two groups: Group1- patients received 2 ml of 0.5 % isobaric levobupivacaine (10 mg) plus 25 microgram fentanyl and Group 2 patients received 2 ml of 0.5 % isobaric levobupivacaine plus 30 microgram clonidine. The vital events and outcome measures were recorded.

Results: The mean HR was lower in group 2 as compared to group1. Blood pressure (SBP, DP, MAP) was higher in group 2 as compared to group 1 at different interval. The mean onset time of group 2 (136.63 ± 25.97 sec.) was significantly lower as compared to group 1 (174.90 ± 27.58 sec.). The time to bromage score 3 was found to be significantly lower in group 2 than group1. The time to achieve maximum sensory level was significantly lower in group 2 than group 1. Two segment regression times was significantly higher (75.53 ± 6.13 min) in group 2 as compared to group 1(66.67 ± 8.74 min). There was no significant difference in the APGAR score in two groups.

Conclusion: It is concluded that spinal anesthesia with isobaric levobupivacaine with clonidine provides fast and effective induction of surgical anesthesia for emergency cesarean section with minimal hemodynamic instability.

INTRODUCTION

Pre-eclampsia is defined as the association of pregnancy induced hypertension with proteinuria of greater than or equal to 300 mg/24 h after 20 weeks of gestation. It is a severe complication of pregnancy leading to fetal morbidity and mortality and has been reported to complicate 4-7 % of all pregnancies. The American college of obstetricians and gynecologists characterized preeclampsia as the development of hypertension with proteinuria, edema or both (the traditional triad) induced by pregnancy after the 20th week of gestation [1,2]

Caesarean section is one of the most common operations in the child bearing age of a woman. Subarachnoid block (SAB) for caesarean section is advantageous because of less neonatal exposure to depressant drugs, decreased risk of maternal pulmonary aspiration and an awaken mother at the birth of her child [3]. Consensus opinion favors regional anesthesia if possible in order to decrease the risks of aspiration and failed intubation in pre-eclampsia parturients [4].

Fentanyl following intrathecal administration does not tend to migrate to fourth ventricle in sufficient concentration to cause delayed respiratory depression [5]. Clonidine a non-opioid α_2 adrenergic agonist, has been used as adjuvant in neuraxial block. Clonidine potentiates sensory and motor block of intrathecal local anaesthetic [6].

Bupivacaine is the most popular local anaesthetic for spinal anaesthesia in parturients undergoing Caesarean section. It is a long acting amide local anaesthetic with duration of action of 1 ½ -2 hours. It is marketed as racemic mixture of the S (-) and R (+) stereoisomers. R (+) component contributes to toxicity [7]. Levobupivacaine, the pure S (−) enantiomer of bupivacaine, emerged as a safer alternative for regional

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anesthesia. Due to its lower cardiovascular side effect and central nervous system toxicity, use of levobupivacaine is progressively increased [8].

The suitable anesthetic technique for patients with pre-eclampsia is still a challenge because both general anesthesia and an epidural block are fraught with pitfalls. Opinions are controversial regarding the use of an epidural in pre-eclampsia patients undergoing caesarean section. Traditional rapid sequence induction of general anesthesia is associated with significant increases in maternal blood pressure. Although this is well tolerated by healthy parturients, it may be detrimental in pre-eclampsia or cardiovascular disease patients.

In our best knowledge, no clinical studies have examined the comparative effects of intrathecal isobaric levobupivacaine with fentanyl and with clonidine in pre-eclampsia patients. Therefore we aim to compare the effects of fentanyl and clonidine as adjunct to isobaric levobupivacaine by intrathecal route.

MATERIAL AND METHODS

This prospective comparative study was carried out at Queen Mary Hospital of King George Medical University, Lucknow U.P.in year July 2014 to august 2015, after obtaining approval from the Ethical Committee. Sixty preeclampsia parturients planned for emergency caesarean delivery under regional anesthesia were included in the study. Informed consent was obtained from all the patients before including in the study.

Patients with 21–39 years age, ASA grade 1 and 2, singleton pregnancy and mild to moderate preeclampsia were included. Patients with severe hypertension, eclampsia, severe hypotension, bradycardia, bleeding diasthesis and those taking anticoagulants, known hypersensitivity to local anaesthetic, patients on drugs like beta blocker and calcium channel blocker, placenta previa, HELLP syndrome, pulmonary edema, cord prolapse and severe fetal distress were excluded from the study.

The study included 60 pre-eclampsia patients scheduled for emergency caesarean section allocated in two groups by using computer generated random number table. Group 1: Spinal anesthesia was given with 2 ml of 0.5 % isobaric levobupivacaine (10 mg) plus 25 microgram fentanyl. Group 2 received 2 ml of 0.5 % isobaric levobupivacaine plus 30 microgram clonidine.

On arrival to operation theatre, intravenous preloading with 10 ml per kg crystalloid was done and premedicated with 4 mg ondansetron intravenously. The patient vitals monitored with automated blood pressure cuff, electrocardiogram, and pulse oximetry. Basic demographic characteristics like age, weight and height were noted. Under all aseptic and antiseptic precautions the subarachnoid block was given at L3-4 interspace via the midline approach using a 25 Gauge Quincke's spinal needle in sitting position. Correct needle placement was confirmed by free flow of cerebrospinal fluid and drug under study injected at the rate of 0.2ml/s. The spinal needle was removed and the patient was placed in supine position with 15 degree left uterine displacement with a wedge under the right flank.

Throughout the procedure, the patient oxygenated at rate of 5 lit. per min through ventimask along with continuous monitoring of electrocardiogram, heart rate, pulse oximetry, and noninvasive arterial blood pressure.

Onset of sensory block was assessed by assessing the changes in pin prick sensation in mid axillary line every 1 min till no sensation (grade 2) is achieved. Onset of Motor block (Bromage scale) was assessed every 1 min till complete motor block is achieved (grade 3). Duration of sensory block was taken as the time from the onset of sensory block to the time of regression to T12 dermatomal level was reached. Duration of motor block (from Bromage scale 3 to grade 1) was taken as the time from complete motor block to when the patient recovers the ability to flex knees i.e. grade 1 on Bromage scale. If level of analgesia was inadequate, or in case of failed anesthesia, the regimen was switched to general anesthesia and excluded from the study also in patients where sensory level of at least T6 was not achieved even after 20 minutes of subarachnoid injection, general anesthesia administered and patient excluded from the study.

Intraoperative continuous monitoring of vitals (HR, SBP and DBP pulse oxymetry) was done, and recorded at regular interval as before spinal anesthesia and then every 2 min for next 20 minutes, and thereafter after every 10 minutes for until completion of surgery and the patient was transferred to the post-operative ward or till 180 min.

Bradycardia was defined as pulse rate < 50 bpm, and it was treated with 0.4 mg IV atropine. Arterial hypotension was defined as a 25% or greater decrease from baseline systolic blood pressure, and was treated with phenylephrine 100µg IV bolus every 2 minutes until blood pressure was restored. Phenylephrine use and total dose were recorded for each patient. Whether there was a need for intraoperative analgesia (25 µg IV fentanyl was used) and time to first analgesic requirement in the postoperative period were recorded. Intraoperative and postoperative nausea and vomiting, and other side effects were recorded.

Statistical analysis

Data was presented as mean±SD and number (percentage) as appropriate. Chi square test or fisher's test was used for qualitative variables. The Unpaired Student's t-test was used to compare between groups for quantitative variables. The p-value <0.05 was considered significant. All the analyses were performed on SPSS software version 16.0 (Chicago, Inc., USA).

RESULTS

There was no significant (p>0.05) difference in the basic characteristics of patients between the groups as shown in Table 1. The mean HR was comparatively lower in group 2 as compared to group 1 at most of the time periods. It was significantly different (p<0.05) between the groups from 16 minutes onwards till 90 minutes (Fig.1).

Table 1 Basic characteristics (Mean ± SD) of two groups

	Group 1 (n=30)	Group 2 (n=30)	p-value[1]
Age (yrs)	28.10 ± 4.36 (20-37)	26.33 ± 3.85 (20-34)	0.102
Weight (kg)	54.83 ± 4.42 (46-62)	54.83 ± 5.24 (46-65)	1.000
Height (cm)	162.60 ± 6.27 (153-174)	163.70 ± 6.39 (150-177)	0.504
BMI (kg/m^2)	20.75 ± 1.45 (18.20-24.52)	20.47 ± 1.71 (17.44-23.88)	0.496

[1]Unpiared t-test, Number in parenthesis indicates the range (min-max)

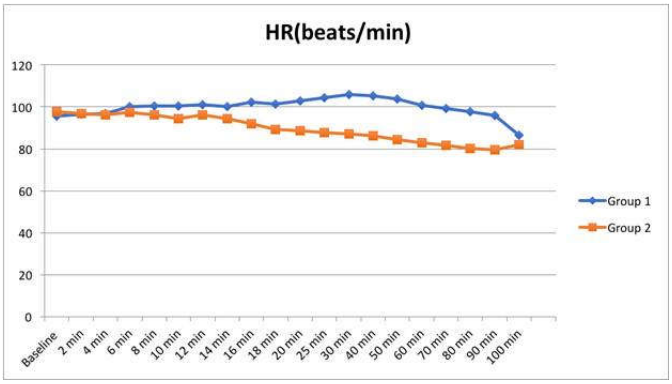

Fig 1 Mean HR of two groups over the time periods

The mean SBP and DBP were comparatively higher in group 2 as compared to group 1 at most of the time intervals. The difference in SBP and DBP between the groups was found to be significant ($p<0.05$) at most of the time periods (Fig. 2, Fig. 3).

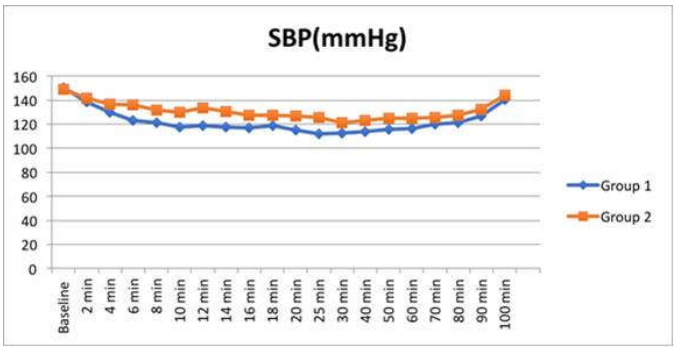

Fig 2 Mean SBP of two groups over the periods

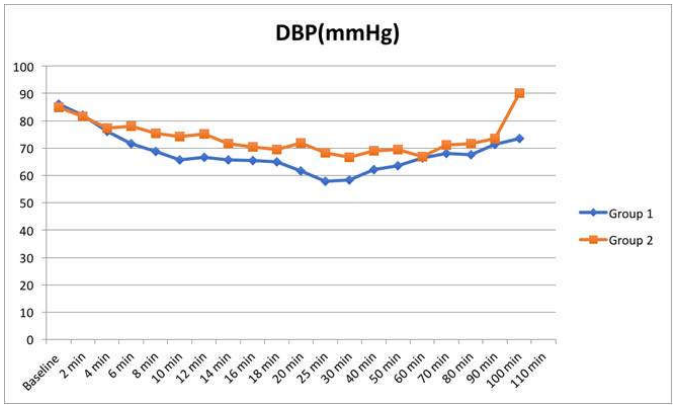

Fig 3 Mean Diastolic blood pressure of two groups

The mean MAP was comparatively higher in group 2 as compared to group 1 at most of the periods. The difference MAP between the groups was found to be statistically significant ($p<0.05$) at most of the time periods from 16 min onwards (Fig. 4). The mean need of rescue vasopressor was less (59%) in group 2 than group 1, but the difference is statistically insignificant. The mean onset time of was significantly ($p=0.001$) lower in group 2 (136.63 ± 25.97 sec.) as compared to group 1 (174.90 ± 27.58 sec.). The time to Bromage 3 was found to be significantly ($p=0.001$) lower (6.80 ± 1.56 min) in group 2 than (8.07 ± 1.36 min) group1. The time for two segment recession were significantly ($p=0.001$) higher (75.53 ± 6.13 min) in group 2 as compared to (66.67 ± 8.74 min) group 1 and regression to T12 segment (171.50 ± 17.57 min.) in group 2 and (153.83 ± 17.50 min.) in group1.There was no significant ($p>0.05$) difference in the APGAR score between the groups at 1, 5 and 10 minutes (Table 2). The nausea was found in 13.3% patients in group 1 and 3.3% in group 2. However, pain was in 6.7% patients in group 1 and in 3.3% in group 2. The difference in the complications was statistically not significant ($p<0.05$).

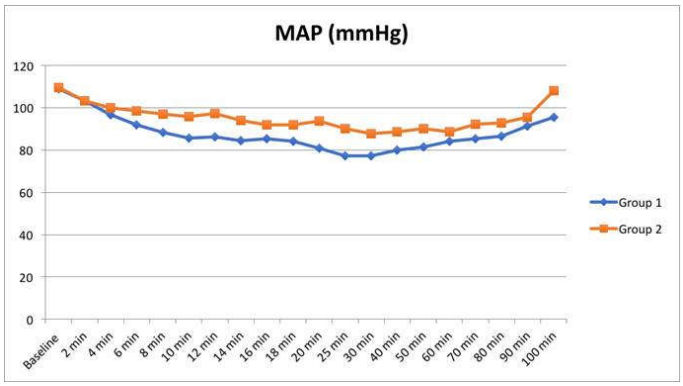

Fig 4 Mean of Mean Arterial Pressure of two groups over periods

Table 2 Comparison of outcome parameters between the groups

	Group 1 (n=30)	Group 2 (n=30)	p-value
Onset of drug effect (sec.)	174.90 ± 27.58	136.63 ± 25.97	0.0001*[a]
Time to Bromage 3 (min.)	8.07 ± 1.36	6.80 ± 1.56	0.001*[a]
Time to achieve sensory level			
T10 min	4.13 ± 0.73	3.33 ± 0.61	0.0001*[a]
T6 min	9.17 ± 1.39	7.20 ± 0.92	0.0001*[a]
T4 min	15.20 ± 1.92	12.27 ± 2.21	0.0001*[a]
Maximum sensory level, no. (%)			
T2	1 (3.3)	0 (0.0)	
T4	26 (86.7)	26 (86.7)	0.56[b]
T6	3 (10.0)	4 (13.3)	
Regression			
Time for 2 segment regressions (min)	66.67 ± 8.74	75.53 ± 6.13	0.0001*[a]
Regression time to T12 (min)	153.83 ± 17.50	171.50 ± 17.57	0.0001*[a]
Regression time for Bromage 0 (min)	113.33 ± 16.88	133.17 ± 19.50	0.0001*[a]
APGAR score			
1 min	6.78 ± 0.42	6.78 ± 0.42	1.00[a]
5 min	7.82 ± 0.39	7.82 ± 0.39	1.00[a]
10 min	8.42 ± 1.64	8.77 ± 0.43	0.11[a]

[a]Unpaired t-test, [b]Chi-square test, *Significant

DISCUSSION

Over the last decade, spinal anesthesia has been redefined with the addition of adjuvants to local anesthetic solutions. The recent research in new adjuvants provide faster onset of action, prolong duration of anesthesia and postoperative analgesia, reduce the doses of local anesthetics required to perform a sufficient dermatomal block intensity necessary for Caesarean section. This reduction in local anesthetic requirements reduces the intensity and duration of motor blockade and allows patients to ambulate faster by dose adjustment.

It has been believed that pre-eclampsia patients may carry a high risk with use of spinal anesthesia owing to possibility of severe hypotension with maternal and fetal consequences because of reduced plasma volume and of need to limit IV fluids to avoid iatrogenic pulmonary edema, so use of spinal anesthesia has not been popular in preeclampsia. In our study, we administered spinal anesthesia safely in preeclampsia parturient. We didn't encounter any case of iatrogenic pulmonary edema with judicious preloading.

In the present study, there was not much variation in baseline heart rate between the two groups. The heart rate was observed to be lower in clonidine group from 4 min onwards, but statistically significant difference in HR was observed from 16 min to 90 min. In our study, it was observed that there was slight increase in heart rate from base line in fentanyl group, whereas decline but stable heart rate in clonidine group. However, our finding is in contrast to the study by Larsen et al. [9]. The decrease in arterial blood pressure after neuraxial block can be minimized by preloading with intravenous crystalloids; our patients were preloaded with 10 ml per kg crystalloid to prevent hypotension. Kriton and Leonides et al. [10] and Neimi [11] demonstrated that 150mcg clonidine is associated with hypotension, sedation and dryness of mouth.
In our study, we have not found hypotension with clonidine, it may be because we have used lower dose of clonidine. Belhadj et al. [12] who found that although intrathecal clonidine 30 µg provides prolong analgesia, but increases the incidence of (maternal) hypotension, and abnormal fetal heart rate (FHR) patterns and its use is thus not recommend, but in contrast we did not found any abnormal FHR or significant maternal hypotension.

In the present study, the level of maximum sensory block (T4/T6) did not differ between the groups. Regression time to two segments from peak level and to T12 was comparatively longer in clonidine group as compared to fentanyl group. The difference in two segment recession time between the two group is statistically significant. There is early onset and longer duration of sensory block in clonidine group than fentanyl group. Contrary to our findings, the previous study done by Larsen et al. [9], who found that clonidine had no effect on the onset time and intensity of spinal anesthesia. Duration of motor block was also prolonged in clonidine group than fentanyl group. Regression time for bromage scale 0 is higher in clonidine group as compared to fentanyl group. Our results are supported by similar findings of previous studies by Chhabra et al. [13], who found that the clonidine has advantage over fentanyl as it increases the duration of subarachnoid block and prolonged the post-operative analgesia.

There were no complications in majority of the patients of both groups in our study. Pain was observed in 2% of the patients in both groups for short period during peritoneal stretch for which only reassurance was given. The addition of intrathecal clonidine (75 µg) to hyperbaric bupivacaine in caesarean section does not produces clinically relevant maternal or neonatal side effects [14].

In our study, APGAR score a predictor of fetal wellbeing was found to be good in both groups. As our study was not primarily focused on foetal and neonatal wellbeing, we measured only neonatal APGAR score at 2, 5 and 10 minutes. As the APGAR scoring system is specific but not very sensitive and fails to detect small fetal effects of maternal arterial hypotension [15-17]

In our study, spinal anesthesia performed with isobaric levobupivacaine and adjuvants clonidine and fentanyl provides fast and effective induction of surgical anesthesia for emergency cesarean section in pre-eclampsia patients with good hemodynamic stability and no side effects. Clonidine has advantage over fentanyl to provide better hemodynamic stability, prolong duration of sensory block, thus less analgesics were required post operatively.

CONCLUSION

Spinal anesthesia with combination of Isobaric levobupivacaine and clonidine could be a good alternative to general anesthesia for cesarean sections in pre-eclampsia patients as it provides early onset, increased duration of block, better hemodynamics stability and less side effects.

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