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Original research article

Efficacy of premixed versus sequential administration of clonidine and bupivacaine in caesarean section: A randomised controlled study

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Abstract

Background and Aims: Subarachnoid block is the most commonly used technique for Caesarean section (CS). Opioids are commonly used as adjuvants and are given premixed with local anesthetics (LA) loaded in a single syringe. In doing so, the density of the hyperbaric solution and also of the adjuvant drugs may be altered, thus affecting the spread of drugs. Administering local anesthetic and the adjuvants separately may minimize the effect of the changes in densities. We aimed to compare block characteristics, intraoperative hemodynamics and post-operative pain relief in parturients undergoing caesarean section after administering hyperbaric bupivacaine and clonidine intrathecally as a mixture and in a sequential manner.

Methods: 60 full-term parturients scheduled for elective caesarean section were divided into two groups on the basis of technique of intrathecal drug administration. Group M received mixture of clonidine (45 mcg) and hyperbaric bupivacaine 0.5% (10 mg) intrathecally, whereas Group B received clonidine (45 mcg) followed by hyperbaric bupivacaine 0.5% (10 mg) through separate syringes. Observational descriptive statistics, independent t test were used as applicable.

Results: Duration of analgesia was significantly longer in Group B (432.60 ± 64.65 min) in which the drug was given sequentially than in Group M (322 ± 23.24 min). Furthermore, the time to achieve highest sensory block and complete motor block was significantly less in Group B without any major hemodynamic instability and neonatal outcome.

Conclusion: When clonidine and hyperbaric bupivacaine were administered in a sequential manner, block characteristics improved significantly compared to the administration of the mixture of the two drugs.

Keywords: Adjuvants, caesarean section, clonidine, hyperbaric bupivacaine, spinal anaesthesia, sequential administration

Introduction

Subarachnoid block (SAB) is one of the most common regional anaesthesia techniques used for caesarean section due to lower incidence of major perioperative complications. Choice of local anaesthetic (LA) utilized in SAB is based on the pharmacologic properties of the drug [1]. Hyperbaric bupivacaine is most commonly used as it produces more predictable block with less side effects. Opioids and non-opioid adjuvants have been added to bupivacaine to increase the duration of effect, provide stable haemodynamics and provide prolonged postoperative analgesia [2]. Intrathecal opioids were most commonly used as they were synergistic with LA. Clonidine, a selective partial agonist of alpha-2 adrenoceptors is one of the drug used as an alternative to opioids. It prolongs both sensory and motor block of LA and reduces analgesic requirement in the postoperative period due to its antihyperalgesic effects [3, 4]. The ability to predict the ultimate level of block during spinal anesthesia is essential to providing adequate anesthesia while minimizing side effects. Many factors have been hypothesized to influence the spread of local anesthetic (LA) solutions within cerebrospinal fluid (CSF) [5], including patient characteristics, physical properties of CSF, injection technique, as well as the dose and properties of the particular local anesthetic solution used. The density (defined as the weight in grams of 1 mL of solution) of the compounds used for intrathecal injection is believed to be a major determinant in controlling the extent of neural blockade. Baricity is the ratio of the density of the local anesthetic solution to the density of CSF and thus determines the spread of the solution after injection. The density of cerebrospinal fluid (CSF) at 37 °C is 1.00059 g/ml [6]. Baricity of clonidine is 0.9930 while that of

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hyperbaric bupivacaine is 1.02360. After addition of clonidine in the same syringe as LA, baricity of the solution comes out to be 1.0189. Alterations in the baricity of a solution to the extent of 0.0006 can alter the spread of LA in CSF [7]. Hyperbaric solutions were more predictable, with greater spread in the direction of gravity and less inter-patient variability. Hence the rationale behind performing this study is to see differences in block characteristics mainly onset of block and duration of block along with determining effects on haemodynamics whilst administering hyperbaric bupivacaine and clonidine in a single syringe or separate syringes.

Materials & Methods

The study was a randomized, parallel group, active controlled trial conducted in sixty parturients with singleton pregnancy of American Society of Anesthesiologists (ASA) II physical status undergoing elective caesarean section under spinal anaesthesia after getting approval from the Institutional Ethical Committee. Patients with any contraindication to subarachnoid block, multiple pregnancy, intrauterine death, known fetal anomaly, severe pregnancy induced hypertension, patient on cardiovascular medications and hypersensitivity to clonidine and local anaesthetics were excluded from the study. All patients underwent preoperative evaluation. All patients were provided with patient information sheet and written informed consent was obtained. Patients were kept fasting overnight and oral ranitidine 150 mg and metoclopramide 10 mg were given on the previous night and on the day of surgery morning. The patients were familiarized with concept of visual analogue scale (VAS) for pain assessment with 0=no pain and 10= worst pain. The patients were randomly allocated into two groups of 30 each by sealed envelope technique.

Group M: 10mg of 0.5% hyperbaric bupivacaine plus clonidine 45 microgram as a mixture in single syringe.
Group B: Clonidine 45 microgram followed by 0.5% hyperbaric bupivacaine 10mg in different syringes.

To avoid manufacturer's difference hyperbaric bupivacaine used was HEAVY ANAWIN and clonidine used was CLONEON manufactured by Neon laboratories. Patients were shifted to operating room where heart rate (HR), non-invasive blood pressure, electrocardiography and oxygen saturation (SpO_2) monitors was connected and baseline parameters were recorded. Patients were preloaded with 15 ml/kg of lactated ringer solution 15-20 min before spinal block. Under strict aseptic precautions and after administration of local anaesthesia using 2ml of 2% lignocaine in the L3-L4 interspace, subarachnoid block was administered using 25 G Quincke needle. All the drugs were injected over a period of 30 seconds, with less than 5 seconds between the change of syringes in group B. After the block, patients were kept in supine position with a 15-20 degree left tilt. An anesthesiologist who was unaware of the drug given evaluated the block characteristics and hemodynamic parameters.
Sensory block was assessed by a sterile pin prick using 23G hypodermic needle every 2 minutes till 20 min and then after every 10 min till highest level is achieved. Onset of sensory blockade is defined as time taken from the completion of the injection of study drug till the loss of pin prick sensation at T10 level. After this the level was tested every 30 minutes until regression from highest level to T10 dermatome was noted. Time taken for maximum sensory blockade: is defined as the time taken from the completion of the injection of the study drug to the maximum sensory blockade attained. Assessment of motor blockade: Will be assessed by the modified Bromage scale:-
0-Able to perform full straight leg raise over the bed for 5 seconds.
1-Unable to perform a leg raise but can flex the leg on the knee.
2-Unable to flex knee but can flex ankle.
3-Unable to flex ankle.
4-Unable to move toes.

Motor block was assessed at the same interval as sensory block. Onset of motor block was assessed by time to reach Bromage score 2 [8]. Time to achieve complete motor block (Bromage 4) and its regression to Bromage 1 was noted.
Vital parameters of the patient were assessed periodically till the completion of the procedure.
Hypotension was defined as decrease of systolic blood pressure to 80% of baseline or less and was treated with 6 mg ephedrine given intravenously.
Bradycardia defined as HR <60 beats per minute was corrected using 0.6 mg of intravenous atropine sulfate. Postoperative need of analgesia in the form of diclofenac or rescue dose of fentanyl was also recorded.
Incidence of complications such as nausea and vomiting and sedation were graded according to the respective scales [9, 10]. The primary outcome of the study was the onset and duration of sensory and motor blockade in minutes while variation in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2), postoperative analgesia for 24 h and patient and surgeon satisfaction scores were taken as secondary

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outcomes.

Results

Demographic data in terms of age, height, weight and duration of surgery were comparable in both groups. They were found to be statistically insignificant [Table 1]. All 60 patients in the two groups completed the study without any exclusion. We did inter group analysis. Of the 60 patients, 30 belongs to Group M [mixture of clonidine 45mcg and hyperbaric bupivacaine 0.5% (10 mg)] and other 30 categorized as Group B [clonidine 45 mcg followed by hyperbaric bupivacaine 0.5% (10 mg)]. Data were presented as maximum, minimum, mean, standard deviation. The probability value 'p' of less than 0.05 was considered as statistically significant.

Table 1: Demographic Profile of Patients

Variables	Group M	Group B	P value
Age (years)	26.20±3.31	25.93±3.03	0.747
Weight (kg)	59.27±2.97	59.87±2.98	0.438
Height (cm)	156.47±4.70	160.73±18.66	0.230
Duration of surgery (min)	79.33±6.98	80.30±1.84	0.466

The onset time of sensory and motor block and also the highest level of block achieved (T5) were comparable in both groups [Table 2]. Mean time to reach maximal cephalad-sensory block height was significantly less in Group B (3.50±0.97 min) than in Group M (4.57±1.94 min) with p value of 0.000 and the total duration of analgesia lasted significantly longer in Group B (432.60±64.65 min) as compared to Group M (322.53±23.24 min) (P=0.000). Complete motor blockade was achieved earlier in Group B (5.03±0.92 min) than in Group M (5.57±1.10 min) (P=0.047).

The resolution time of motor block was significantly prolonged in Group B (286.03±16.90 min) than in Group M (199.77±38.23 min), P=0.000.

Table 2: Block Characteristics

Variables	Group M	Group B	P value
Onset of sensory block (sec)	65.03±10.38	61.93±0.404	0.115
Maximum sensory block height (T), median	T4(T3-T5)	T4(T3-T5)	NS
Time to reach maximum cephalad sensory block height (min)	4.57±1.94	3.50±0.97	0.000
Regression time to T10 (min)	162.03±11.62	238.67±27.90	0.000
Total duration of analgesia (min)	322.53±23.24	432.60±64.65	0.000
Onset time of motor block (min)	2.80±1.06	2.47±0.77	0.171
Time to complete motor block (min)	5.57±1.10	5.03±0.92	0.047
Resolution time of motor block (min)	199.77±38.23	286.03±16.90	0.000

There is a significant fall in SBP at 2 min and 4 min after administration of SAB in both groups.

A significant fall in DBP was seen at 2, 4, 6, and 8 min of administration of SAB. There was an overall trend of fall in SBP and DBP in both groups, except during the time intervals of 20 and 25 min (during delivery of baby) where there was rise in both SBP and DBP. The falling trend of arterial blood pressures was more in the Group B than in Group M and it was found to be statistically insignificant. No incidents of bradycardia were recorded.

Patients complaining of nausea or vomiting were given injection ondansetron 0.15mg/kg IV. Any complaints of dry mouth was noted. Newborn APGAR scores were determined by a paediatrician not otherwise involved in the study at 1, 5, and 10 minutes of birth.

Post-operatively any incidence of bradycardia, hypotension, nausea, vomiting was noted and treated accordingly. They were asked about the presence of headache (PDPH), back pain, numbness and tingling sensation in the lower extremities. The data collected was transformed into a master sheet one for each group. Data entry was done using SPSS 21 for Windows. Descriptive statistics like percentages, mean with standard deviation and 95% confidence interval were used. Statistical analysis was done by Student's t test for quantitative data and Chi Square test for qualitative data. The incidence of complications between the groups M and B and was found to be comparable in both the groups. It is found that hypotension was present in 8(26.7%) and 10(33.3%) of the patients in group M and group B respectively and vasopressor was used in 1 patient among group M and 3 patients in group B. Vomiting was present in 5(16.7%) and 9(30.0%) of the patients respectively.

Discussion

We conducted a randomized controlled study to evaluate the efficacy of premixed versus sequential administration of clonidine as an adjuvant to hyperbaric bupivacaine intrathecally in caesarean section. Background of the study was mixing adjuvants with hyperbaric bupivacaine in a single syringe before injecting the drugs intrathecally is an age old practice. In doing so, the density of the hyperbaric solution

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and also of the adjuvant drugs may be altered, thus affecting the spread of drugs. Administering local anesthetic and the adjuvants separately may minimise the effect of the changes in densities. The observation and results obtained in the study are based on the assumption that the original densities of hyperbaric bupivacaine and clonidine are lost when they are premixed in a syringe thus exerting suboptimal actions when compared to sequential manner of administering the drugs. Our assumption is supported by the work of Prachee Sachan *et al*., [11] who conducted a randomised controlled study in caesarean section by administering intrathecal clonidine with hyperbaric bupivacaine as a mixture and sequentially and Desai *et al*., [8] who studied the same effect by adding opioids to local anaesthetic solution intrathecally in caesarean section.

Intrathecal clonidine ranging from 15 mcg to 300 mcg along with local anaesthetics has been used by many authors. Kaabachi *et al*., [12] used 2 mcg /kg of intrathecal clonidine in their study and reported prolonged duration of post-operative analgesia, but with moderate side effects. 70 mcg of clonidine was used by Sethi *et al*., [13] and found a significant decrease in mean arterial pressure and heart rate in clonidine group, but none of them required therapeutic intervention.

A recent study by Ranju Singh *et al*., [14] on intrathecal clonidine with hyperbaric bupivacaine in caesarean section showed that a dose of 75 mcg clonidine increased the duration of analgesia significantly without increasing maternal side effects.

Similarly van Tuijl *et al*., [15] demonstrated that addition of 75 mcg of clonidine to hyperbaric bupivacaine prolongs spinal analgesia and the motor block in caesarean section without maternal or neonatal side effects. We used 45 mcg of clonidine and found that it helps in achieving a faster block and longer duration of action without much hemodynamic variability or side effects.

The densities of the drugs that we used separately (hyperbaric bupivacaine and clonidine) were 1.0260 and 0.9930, respectively. The density of the mixture of 2 ml (10 mg) of hyperbaric bupivacaine and 0.3 ml (45 mcg) clonidine was also estimated and it was found to be 1.0189.

In our study, we noticed that the mean onset time of sensory and motor block was similar in both groups but the onset of sensory block does not get any better after a particular dose which was supported by a study done by Heo *et al*., [16] who did not report any difference in onset time of sensory or motor block even after using 150 mcg clonidine. The time to reach maximum sensory block height and a complete motor block was significantly less in Group B (sequential drugs) than in Group M (mixed drugs) in our study. This difference might have existed because of the preferential cephalad spread of clonidine when we administered it through a separate syringe, owing to its hypobaric nature which was lost when the drugs were premixed.

In our study, we found that the mean time taken for regression of sensory block to T10 level was significantly longer in Group B (238.67 ± 27.90 min) than in Group M (162.03 ± 11.62 min) and mean time taken for motor block regression also significantly longer in Group B (286.03±16.90 min) than in Group M (199.77±38.23 min). Similarly, the mean duration of analgesia significantly prolonged in Group B (432.60 ± 64.65 min) than in Group M (322.53 ± 23.24 min), depicting significant prolongation of analgesic effect in the group receiving drugs in a sequential fashion.

This difference might be due to the fact that injecting clonidine and bupivacaine as a mixture dilutes clonidine and receptor occupancy might decrease leading to less pronounced effect. However, if clonidine is administered separately, we expect a greater spread and therefore formation of stronger bonds with the receptor leading to a denser and prolonged block.

Desai *et al*., [8] found that dextrose in a hyperbaric solution slow the movement of morphine molecules in the CSF, reducing the exposure of supraspinal centres to morphine. Clonidine due to its hypobaric nature, acting on both spinal and supraspinal receptors, might exhibit similar properties. Gray *et al*., [17] observed that duration of analgesia is prolonged when intrathecal morphine is administered with normal saline (hypobaric) than with dextrose saline (hyperbaric).

Activation of post-synaptic alpha-2 receptors in the substantia gelatinosa of the spinal cord is the presumed mechanism by which clonidine produces analgesia. These receptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial lamina of the spinal cord, and within several brainstem nuclei implicated in analgesia, supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites.[15,18] decrease in heart rate after clonidine administration caused by a presynaptic mediated inhibition of norepinephrine release and by a direct depression of atrioventricular nodal conduction after systemic absorption. The maximum fall in the heart rate when compared to the baseline was 19% in Group B, whereas it was only 12% in Group M which was statistically significant (p<0.001). This fall in heart rate was more pronounced after about 40-60 min of administration of subarachnoid block and towards end of the surgery. However, in our study bradycardia has not been recorded.

In our study a significant fall in arterial blood pressure after subarachnoid block was observed. The fall from baseline SAP and DAP in Group M was 10% and 14% and in Group B was 8% and 13%, respectively. Hemodynamic effects of clonidine after neuraxial or systemic administration begin within 30 min, reach maximum within 1-2 h, and last approximately 6-8 h after a single injection.

Hypotension was noticed in 26.7% of patients in group M and 33.3% of patient in group B in our study,

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which was managed by intravenous fluids and vasopressors were needed for only 1% and 3% parturients in Groups M and B, respectively which was comparable in both groups, suggesting that the clonidine groups did not have a higher predisposition for the development of significant hypotension if administered sequentially than mixed groups. In our study, the level of sedation provided by intrathecal clonidine (RSS 2 and 3) was not only acceptable, but also beneficial owing to its anxiolytic effects.
Benhamou *et al*. [19] found that when intrathecal clonidine was administered with hyperbaric bupivacaine, none of patients required additional analgesics to obtain an adequate sensory block. None of the patients complained of dry mouth. Similarly in our study none of them required additional analgesics during intra operative period. There was no incidence of hypotension, bradycardia and nausea/vomiting, neurological deficit, prolonged sedation, in the post-operative period.
The APGAR scores in our study were comparable in both groups. Benhamou *et al*. [19] and Neves *et al*. [20] also concluded that addition of intrathecal clonidine did not adversely affect the neonatal outcome in terms of APGAR scores. In our study, we measured the densities of solutions *in vitro* but, we could not measure the densities when injected into the CSF. Hence, we could not assess what actually happens to the drug densities intrathecally. Similarly, effect of temperature of drugs when injected were not considered.

Conclusion

We conclude that administering clonidine first followed by hyperbaric bupivacaine leads to early onset and prolonged duration of sensory and motor block and it significantly prolongs the post-operative analgesia. Both groups provided dense analgesia. Sedation was not increased in the sequential technique. The incidence of hypotension or bradycardia was comparable in both techniques. Neonatal outcome remained unchanged in both.

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