

**Original article:**

## **Intrathecal clonidine with hyperbaric bupivacaine administered as a mixture and sequentially in caesarean section: a randomized control study**

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### **ABSTRACT:**

**INTRODUCTION:** Since adjuvants are being mixed with local anaesthetics in a single syringe. Mixing might change the density of the drug solution and the adjuvant, whereby affecting the spread of the drug in the cerebrospinal fluid. Administering adjuvant and local anaesthetics separately might help reduce the effect of change in density.

**OBJECTIVES:** To study block characteristics, intraoperative haemodynamics and postoperative pain relief in parturients posted for elective caesarean section by administering clonidine and hyperbaric bupivacaine as a mixture and sequentially.

**METHODS:** A single blind randomized study was carried out in 100 parturients scheduled for elective caesarean section. They were divided in to two groups randomly on the basis of the technique of intrathecal drug administered. Group M received mixture of 75 mcg clonidine with 10 mg hyperbaric bupivacaine 0.5% while group B received clonidine and hyperbaric bupivacaine separately in two syringes. The onset, time to reach peak sensory and motor level, duration of sensory and motor block, duration of analgesia, effect on new-born outcome and complications, if any were recorded.

**RESULTS:** Mean onset of motor block was significantly ( $p= 0.025$ ) faster in group B ( $1.80 \pm 0.23$  mins) than in group M ( $1.91 \pm 0.25$  mins). Time to achieve highest level of sensory and motor block was faster and duration of sensory and motor block was also significantly longer in group B. Duration of analgesia was significantly more in group B,  $378.50 \pm 17.21$  mins than in group M  $234.52 \pm 25.97$  mins ( $p<0.001$ ), without any major hemodynamic instability, adverse new born outcome and complications. **CONCLUSION:** Administering clonidine and hyperbaric bupivacaine intrathecally sequentially improves the block characteristics and prolongs duration of analgesia significantly compared to administering as a mixture.

**KEYWORDS:** adjuvants, clonidine, hyperbaric bupivacaine, spinal anaesthesia.

### **Introduction:**

Regional blocks remain a well-accepted component of comprehensive anesthetic care which avoids unwanted effects of anesthetic drugs used in general anesthesia, the stress of laryngoscopy and tracheal

intubation. Spinal anesthesia has been widely used as a safe anesthetic technique for caesarean sections due to greater maternal safety, fetal benefits, higher parental satisfaction and consumer demand(1). However, to improve the quality of analgesia various adjuvants are added intrathecally with local anesthetics(2)(3). Hyperbaric bupivacaine is the most commonly used local anesthetic drug in spinal anesthesia. Clonidine, a selective partial agonist for alpha-2 adrenoceptors, is an attractive alternative to commonly used opioids. Adjuvants are mixed in a single syringe before administering the drug intrathecally(4)(5)(6). Mixing of these drugs changes the density of both the drugs, thus affecting the spread in cerebrospinal fluid(5)(7). Density is known to influence the spread of local anesthetic but the effect of adjuvant solution density on its movement in cerebrospinal fluid has not been studied extensively.

Therefore, we hypothesized that administering local anesthetic and adjuvants separately may minimize the effect of changes in densities and hence their actions. In our study we compared the block characteristics, intraoperative haemodynamics and post-operative pain relief in parturients undergoing caesarean section after administering hyperbaric bupivacaine and clonidine intrathecally as a mixture and sequentially.

#### **Methods:**

After the institutional ethics committee approval and written informed consent, 100 parturients in the age group of 20 to 35 years, with singleton pregnancy, belonging to American society of anaesthesiologist physical status 1 and 2, scheduled for elective caesarean section under subarachnoid block were enrolled in this single blind prospective randomized controlled trial. Parturients with multiple pregnancy, known fetal anomaly, fetal distress, severe pregnancy induced hypertension, any contraindication to subarachnoid block, patients on cardiovascular medications, patients who were known case of diabetes mellitus, ischemic heart disease, arrhythmias and who had history of hypersensitivity to clonidine or bupivacaine were excluded from the study. Parturients, were randomly allocated to one of the groups.

Parturients in group M ( $n=50$ ) received hyperbaric bupivacaine (0.5%) 10 mg (2 ml) and clonidine 75 mcg (0.5 ml) as a mixture. Group b ( $n=50$ ) received clonidine 75 mcg (0.5 ml) followed by hyperbaric (0.5%) 10 mg (2 ml) in different syringes. For our study, we used heavy bupivacaine 0.5% and preservative free clonidine (cloneon). Patients were kept fasting overnight. They were familiarized with the concept of visual analogue scoring (VAS). Injection (Inj) ondansetron 0.08 mg/kg intravenous (iv) and Inj ranitidine 1 mg/kg iv was given as antacid prophylaxis to them on the morning of day of surgery.

Intraoperative monitoring for heart rate, non-invasive blood pressure, electrocardiography, oxygen saturation ( $SpO_2$ ) was connected and base line parameters were recorded. Venous access was established with 18-gauge cannula and parturients were pre-loaded with 15 ml/kg of lactated ringer's solution 15-20 mins before spinal block. Under all aseptic precautions subarachnoid block was administered with 25 gauge Quincke's spinal needle in sitting position through the midline approach. Intrathecal drug was administered in L3-L4 space over 30 secs (including the time for change of syringe in sequential administration), after free clear adequate cerebrospinal fluid flow was observed and intrathecal space confirmed. After the block was performed, the patients were made supine with 15°-20° left displacement of uterus until birth of baby by keeping a wedge under the right buttock. An experienced anaesthesiologist

who was unaware of the drug given evaluated the physiological parameters and the spinal block. Ringer's lactate was used as maintenance fluid at the rate of 10 ml/kg/hour. Zero time was defined as time of injection of local anesthetic.

Hemodynamic parameters such as heart rate(HR), systolic arterial blood pressure(SAP), diastolic arterial blood pressure(DAP) were monitored every 2 min for the first 20 mins and then every 5 min subsequently until 75 mins or completion of surgery. Any episode of bradycardia or hypotension within 24 hours was noted. Hypotension was defined as decrease in systolic arterial pressure below 90 mmHg or a fall in blood pressure by >20% of baseline. It was treated with a rapid infusion of crystalloid(200ml) and a bolus of Inj. mephranamine 6 mg iv if it persisted. Bradycardia (HR <50) was treated with Inj. glycopyrolate 0.2 mg iv or inj. atropine 10 mcg/kg iv if it persisted. Respiration was monitored. Respiratory depression was defined as respiratory rate <10 or spo<sub>2</sub><92% following which oxygen was supplemented through nasal prongs @4 lit/min.

Onset of sensory block was assessed by loss of pin prick sensation along mid-clavicular line bilaterally. Dermatome level was checked every 2 mins after subarachnoid block, until level was achieved for four consecutive readings. Time from intrathecal injection to highest sensory level (maximum block height) was also noted. Sensory level was tested every 30 mins till regression of block to T10 dermatome level. It was graded as grade 0-sharp pin felt, grade 1-analgesia, dull sensation, grade 2-anesthesia, no sensation. Onset of sensory block was defined as the time between injection of drug and total absence of sensation. Duration of block was the time between onset to recovery i.e dull sensation felt. Motor block was assessed by modified Bromage scales below grade 0-no motor block, grade 1- free movement of legs and feet, grade 2-just able to flex knees with free movement of feet, grade 3-unable to flex knees but with free movement of feet, grade 4-unable to move legs and feet. Onset of motor block was defined as the time to reach modified Bromage grade 2. Time to achieve complete motor block (grade 4) and its regression to grade 1 was also noted.

Sedation score was assessed by Ramsay Sedation Score (RSS) at the same interval as sensory block until 2 hours postoperatively; as level 1-awake, anxious, agitated, restlessness; level 2- awake, tranquil, cooperative; level 3-responds to commands; level 4-asleep, brisk response to stimuli; level 5- asleep sluggish response to stimuli and level 6-asleep, no response to stimuli. Intraoperative pain was assessed and expressed as VAS.

Duration of effective analgesia was assessed to be the time from intrathecal injection till VAS score was  $\geq 3$ , when rescue analgesia in the form of injection diclofenac 75 mg intramuscularly was administered. Patients complaining of nausea or having any episode of vomiting were given injection ondansetron 0.15 mg/kg i.v. New born outcome was assessed by new born Apgar score at birth by the pediatrician, not otherwise involved in the study at 1, 5 and 10 mins. Post-operative incidence of bradycardia, hypotension, nausea/vomiting, prolonged sedation reported by the post-operative care unit staff was taken into account and managed accordingly.

Statistical analysis was done by using spss (statistical package for social sciences) version 20.0 and Microsoft Excel. Statistical significance was considered at  $p < 0.05$  and highly significant if  $p < 0.01$ .

**Results**

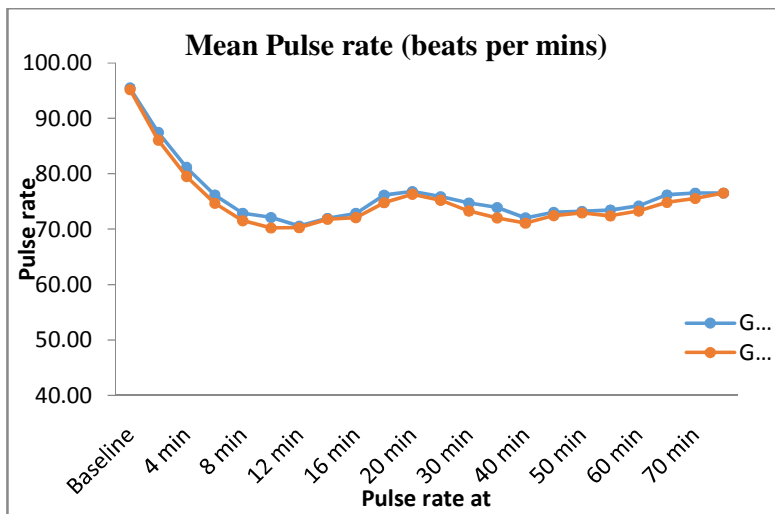
All the 100 patients in both the groups were comparable in terms of age, weight height, ASA grading and duration of surgery (table no 1).

**Table no 1. Showing demographic features of both the groups**

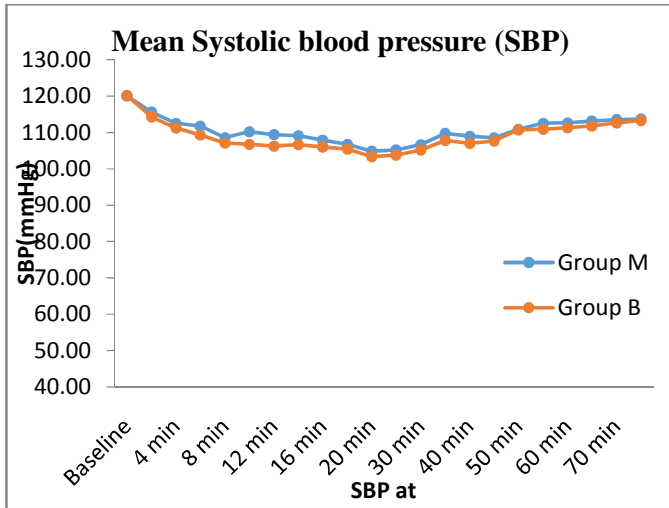
Variables	Group m (n=50)	Group b (n=50)	P value
Age(years)	24.34±2.08	24.82±2.01	0.243
Weight(kg)	57.20±2.96	57.56±3.16	0.558
Height(cms)	155.56±1.34	155.80±1.75	0.444
Duration of surgery(mins)	67.52±5.25	67.66±4.37	0.885

The baseline hemodynamic parameters were also comparable in both the groups. There was significant difference in mean pulse rate in both the groups from 4 to 10 mins after induction. There was a fall in mean heart rate till 10 mins in both the groups M and B after giving intrathecal drug. The falling trend of pulse rate was more in group B (clonidine given sequentially) than in group M (Graph 1). There was a significant fall in mean systolic blood pressure at 6,8,10 and 12 mins in both the groups after giving subarachnoid block. A falling trend of both mean systolic and mean diastolic blood pressure was observed in both the groups after giving spinal block. But the fall was seen to be more in group B (graph 2). Hypotension was observed in 36% parturients in group M as compared to 42 % in group B, which was not significant.

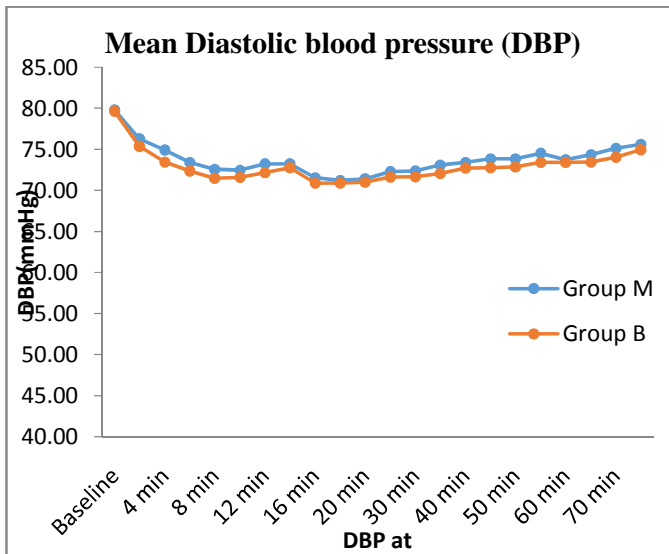
**Graph no 1-Graphical representation of comparison of pulse rate in group M and B**



**Graph no 2- Graphical representation of comparison of mean systolic blood pressure (mmhg) in group M and B**



**Graph no 3 :graphical representation of comparison of mean diastolic blood pressure (mmhg) in group m and b**

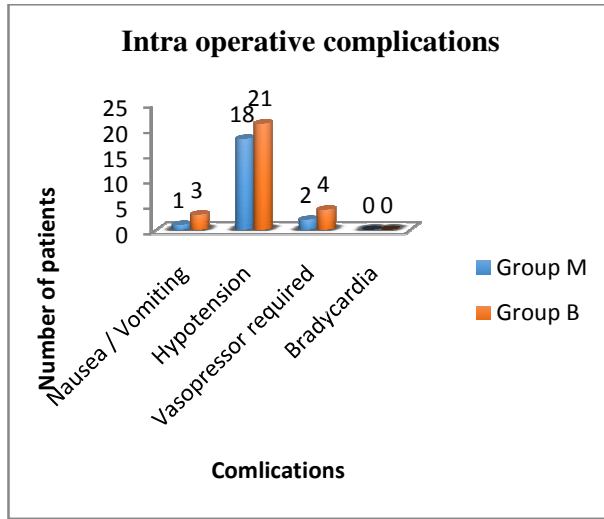


**Table no 2. Comparing block characteristics in both the groups**

Variables	Group m (n=50)	Group b (n=50)	P value
Onset of sensory block(sec)	63.26±2.77	62.68±1.96	Ns
Onset of motor block(min)	1.91±0.25	1.80±0.23	<b>0.025</b>
Maximum sensory block height	T4	T4	<b>Ns</b>
Time to reach highest sensory block(min)	3.73±0.34	3.52±0.31	<b>0.002</b>
Time to reach complete motor block(min)	4.18±0.25	3.95±0.27	<b>&lt;0.001</b>
Duration of sensory block(min)	128.58±6.60	276.30±10.14	<b>&lt;0.001</b>
Duration of motor block (min)	171.22±9.39	313.44±18.20	<b>&lt;0.001</b>
Duration of analgesia(min)	234.52±25.97	378.50±17.21	<b>&lt;0.001</b>
Regression time(min)			

Mean ( $\pm$  SD) onset of sensory block was comparable in both the groups. Mean onset of motor block was significantly ( $p= 0.025$ ) faster in group B ( $1.80 \pm 0.23$  mins) which received clonidine and bupivacaine sequentially than in group m where drugs were given as a mixture. Time needed to reach highest sensory level i.e. T4 level was significantly ( $p<0.05$ ) less in group B ( $3.52 \pm 0.31$  mins) as compared to ( $3.73 \pm 0.34$  mins). Time needed to reach complete motor was also faster in group Bas compared to group M which is also highly significant ( $p<0.001$ ). Mean duration of sensory block i.e time for sensory block to regress to T10 dermatome was highly significantly longer in group B ( $276.30 \pm 10.14$  mins) than in group M ( $128.58 \pm 6.60$  mins). Also duration of motor block was significantly longer in group B ( $313.44 \pm 18.20$  mins) as compared to group M ( $171.22 \pm 9.39$  mins) ( $p<0.01$ ). The duration of analgesia was significantly more in group B than in group M ( $p<0.001$ ).

**Graph no 4- Graphical representation of intraoperative complications in group M and group B**



The incidence of complications like nausea, vomiting, hypotension, bradycardia was comparable in both groups ( $p>0.05$ ). None of the parturients developed any of the complications in the postoperative period. None of the patients had a Ramsay Sedation Score more than 4. In group M only one patient had sedation score of 4 while in group B 3 patients had a score of 4. The apgar scores of neonate at 1,5 and 10 mins; were comparable in both the groups

**Discussion:**

Regional anaesthesia has evolved substantially as anaesthetic technique of choice in parturients, owing to its less maternal and fetal morbidity and mortality(8). Its safety, ease of performing and better maternal satisfaction makes spinal anaesthesia a better choice. Hyperbaric bupivacaine is the most commonly used local anaesthetic for spinal anaesthesia in caesarean sections. Adjuvants like vasoconstrictors (epinephrine), opioids(fentanyl),  $\alpha_2$  agonists (clonidine, dexmedetomidine), NMDA receptor antagonist (ketamine), cholinergic agonist (neostigmine) have been used intrathecally as an adjuvant to local anaesthetic(2)(9). The adjuvant drug acts at a secondary site of action different from that of local anaesthetic.

Clonidine is one of the commonly used adjuvants intrathecally as it is free of opioid related side effects and has antihyperalgesic effects which helps in reducing postoperative analgesic requirement(10)(11)(12). Clonidine is a selective partial  $\alpha_2$  adrenergic agonist ( $\alpha_2$ :  $\alpha_1$  :: 220:1). It has been shown that epidural and spinal administration of clonidine in surgical patients enhances quality and duration of neuraxial anaesthesia, reduces dose of local anaesthetics as well as others neuraxial additives such as opioids. It also increases the duration of postoperative analgesia, and lowers the requirement of systemic postoperative analgesics.

The anatomical site of action of the alpha-2 agonists involves specific receptors of the spinal dorsal horn and supraspinally in the nucleus coeruleus in the pons. Activation of post-synaptic alpha-2 receptors in the substantia gelatinosa of the spinal cord is the presumed mechanism by

which clonidine produces analgesia. The mechanism and location of action of the sedative effect of these compounds are due to the hyperpolarization of excitable neurons localized in the nucleus coeruleus. Alpha 2 agonists induce analgesia by acting in different places; brain, brain stem, spinal cord and peripheral nerves. Their supraspinal analgesic mechanism in the locus coeruleus is probably by transduction, while in the spinal cord is likely related to activation of the descending medullospinal noradrenergic pathways or to the reduction of spinal sympathetic outflow at presynaptic ganglionic sites. Clonidine suppresses the generation of action potentials in tonic-firing spinal dorsal horn neurons. This may be explained, in part, by an interaction with voltage-gated  $na^+$  and  $k^+$  currents. Clonidine also acts synergistically with local anaesthetics because of its action of opening potassium channels(13)

It is a common practice to mix adjuvants and the local anaesthetic in a single syringe prior to injecting the drugs intrathecally. This might affect the density of both the drugs and the solution and hence their spread in the csf. This has been taken into account in various studies(14)(15).

Physical characteristics of spinal anaesthetic solution i.e. Density, baricity and specific gravity are the major determinants of their spread in the csf(5)(73).Density of anaesthetic solution plays a major role. Effect of adjuvant solution density on movement of local anaesthetic in csf and its effect on spinal block and its characteristic has not been evaluated extensively.

As clonidine is an accepted intrathecal adjuvant with local anaesthetic, we used clonidine for our study. We hypothesized that administering local anaesthetic and adjuvant separately might minimize the effect of change in density. Clonidine has been extensively used in the doses of 1mcg/kg - 2 mcg/kg intrathecally. There is no standard dose for intrathecal clonidine(13).Sethi et al(10), used 70 mcg of intrathecal clonidine and found a significant decrease in mean arterial pressure and heart rate in clonidine group, but no therapeutic intervention was required for either. Bhure et al(17) also used 75 mcg of intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in caesarean section and found statistically insignificant hypotension. Strebel et al(18) used 150 mcg of intrathecal clonidine and found prolonged duration of spinal anaesthesia and analgesia, but it was associated with hemodynamic instability.

Niemi et al(19)used 3 mcg/kg of clonidine in their study on patients undergoing knee arthroscopy and reported marked hemodynamic changes in the study group.Hence we chose 75 mcg of intrathecal clonidine dose.We selected parturients undergoing caesarean section as our study subjects as providing a good and longer postoperative pain free period improves both the maternal and the fetal outcome, provides better maternal satisfaction, reduces hospital stay length and better neonatal outcome(8).

In our study, we observed that mean onset of sensory block was comparable in both the groups. This was consistent with Sachan et al(4), who also used 75 mcg of clonidine as adjuvant, as a mixture and sequentially to hyperbaric bupivacaine in caesarean section and found faster onset of sensory block in the group which received clonidine sequentially, but it was also not statistically significant. Kothari et al(20) in their study ,where they compared 12.5 mg 0.5% hyperbaric bupivacaine , 8 mg 0.5% hyperbaric bupivacaine along with 50 mcg clonidine and 10 mg 0.5%



hyperbaric bupivacaine along with 50 mcg clonidine found faster onset of sensory block in group receiving higher doses of bupivacaine. They stated that onset of sensory block depends on the dose of bupivacaine. In our study, as both the group received same amount of hyperbaric bupivacaine (10 mg), this could have been the reason for comparable onset of sensory block. On the contrary the mean onset of motor block i.e. time to attain bromage 2 was significantly ( $p=0.025$ ) faster in group b which received clonidine and bupivacaine sequentially than in group m where drugs were given as a mixture. In a similar study Bansal et al(6) also found mean onset of motor block to be delayed in patients when intrathecal fentanyl was given as a mixture. This was in contrast to Sachan et al(21) who found it to be comparable in both the groups receiving clonidine as a mixture and sequentially.

It was seen that time needed to reach highest sensory level i.e. T4 level and maximum motor block was significantly ( $p<0.05$ ) less in group B as compared to group M. This difference might have existed because of the preferential cephalad spread of clonidine when we administered it through a separate syringe before giving hyperbaric bupivacaine, where in it retained its hypobaric property. The hypobaric nature of clonidine is lost when the drugs are premixed.

Desai et al(15) also observed that the time required to reach highest level of sensory block was less when morphine and fentanyl were administered sequentially with hyperbaric bupivacaine than when given as a mixture. Chaudhary et al(20) determined the efficacy of premixed versus sequential administration of dexmedetomidine as an adjuvant to intrathecal hyperbaric bupivacaine in lower limb surgery and found time required to achieve highest sensory block was lesser when dexmedetomidine was given sequentially.

The mean duration of sensory block i.e. time for sensory block to regress to T10 dermatome was highly significantly longer in group B than in group M. Similarly, duration of analgesia was significantly more in group B than in group M. Mixing clonidine with hyperbaric bupivacaine dilutes the clonidine, hence the number of receptors being blocked by clonidine decreases. When clonidine is given in a separate syringe, the number of receptors occupied by clonidine increases and hence provide a prolonged duration of sensory block.

Jyoti et al(22) in their study between premixed and sequential administration of intrathecal clonidine with hyperbaric bupivacaine in lower limb orthopaedic surgeries also reported that the duration of sensory block is enhanced when clonidine is given sequentially. Sharma et al(23) carried a similar study in caesarean section, and found the duration of sensory block in the group which received intrathecal clonidine sequentially to be  $242.4\pm 16.4$  mins and when given as premixed to be  $148.6\pm 12.12$  mins. This was similar to our study. Desai et al(15) found that duration of analgesia is increased when intrathecal morphine is administered with normal saline (hypobaric) than with dextrose saline (hyperbaric). They explained that dextrose in a hyperbaric solution slow the movement of morphine molecules in the csf, reducing the exposure of supraspinal centers to morphine. Clonidine is also a hypobaric drug. Mixing the drug with hyperbaric bupivacaine (which contains dextrose) slows its movement in the csf. This might affect the spread of drug to the supraspinal centers, which are known for the analgesic effects of

clonidine. Similar observations were made by Jyoti et al(22) in lower limb orthopedic surgeries and Thakur et al(24) in inguinal herniorrhaphy surgeries. They also reported that sequential clonidine significantly increase the duration of analgesia than when it is given in mixture with hyperbaric bupivacaine.

There was significant difference in mean pulse rate in both the groups from 4 to 10 mins after induction. There was a fall in mean heart rate till 10 mins in both the groups M and B after giving intrathecal drug. This could have been due to relief in the pain and anxiety of the patient and sedative effect of clonidine. It was followed by a slight rise in pulse rate seen around 18-20 mins, which coincided with delivery of the baby. The falling trend of pulse rate was more in group B (clonidine given sequentially) than in group M (graph no 1). Clonidine is known to decrease heart rate by a presynaptic mediated inhibition of norepinephrine release and by direct depression of atrioventricular nodal conduction and this decrease correlates with plasma clonidine concentrations. Although there was statistically significant fall in the pulse rate in group B, it was clinically insignificant and no patient developed significant bradycardia intraoperatively.

Sharma et al(23) in a comparative study of pre-mixed and sequential intrathecal administration of clonidine with hyperbaric bupivacaine in caesarean sections also did not report any incidence of bradycardia. There was a significant fall in mean systolic blood pressure at 6,8,10 and 12 mins and in mean diastolic blood pressure at 4 and 8 mins in both the groups. This could have been due to the sympatholytic action of bupivacaine and not clonidine, as hemodynamic effects of clonidine occur after 30 mins of spinal block. Hypotension was observed in 36% parturients in group M as compared to 42% in group B, which was not significant. Also it was not clinically significant as it was easily managed by giving 200 ml of intravenous ringer lactate. Vasopressor was needed in only 4% and 8% of the parturients in group M and B respectively, which was also not significant (graph no 4).

Although intrathecal clonidine is known to cause hypotension, but it was not significant in our study. This could be due to preloading done preoperatively with ringer lactate and provision of wedge below the right hip of the parturients after performing subarachnoid block.

Sachan et al(4) reported hypotension in 13% patients in group that received mixture of intrathecal clonidine and bupivacaine and 16% patient in group which received clonidine and bupivacaine sequentially. They also reported the use of vasopressor in 1% and 3% in both these groups respectively.

Parturients in group M were more sedated than group B, but none of them had Ramsay Sedation Score more than 4. Also all the parturient were comfortable in their postoperative period. Intrathecal clonidine mediates sedation through its action on alpha 2 receptors. The locus coeruleus and the dorsal raphe nucleus are important central neural structures where this drug acts producing sedation. The apgar scores of neonate at 1,5 and 10 mins were comparable in both the groups clonidine had no adverse effect on the newborn outcome, whether given sequentially or as a mixture with hyperbaric bupivacaine.

There was although incidence of hypotension, nausea, vomiting and bradycardia more in group b than in group m but it was not statistically and clinically significant. None of the parturients developed any of the complications in the postoperative period.

The limitation of our study was that we could not measure the densities of solutions when injected into the cerebrospinal fluid. Hence, we could not assess what actually happens to the drug densities intrathecally. Also, effects of temperature of drugs when injected were not considered.

**Conclusion:**

Giving intrathecal clonidine and hyperbaric bupivacaine without mixing in a single syringe reduces the time to attain sensory and motor block and prolongs the duration of block and provides a longer period of analgesia significantly. Sequential technique did not increase the level of sedation and incidence of hypotension or bradycardia as compared to the administration of drugs as a mixture. New-born outcome remained unaffected.

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