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Original Research Article

# A comparative clinical study of intrathecal fentanyl and clonidine with hyperbaric bupivacaine in lower segment caesarean section

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ABSTRACT

**Aims and Objective:** To compare between clonidine and fentanyl as adjuvants with intrathecal bupivacaine in LSCS patients to know the: 1) Starting time and total time of sensory block; 2) Starting time and total time of motor block; 3) Total time of postoperative analgesia.
**Materials and Methods:** In a prospective, randomized study, 120 patients who are to undergo caesarean section between 18 and 30 years of age and of ASA grade I or II were randomly distributed into three groups. Patients were given intrathecally 2 ml of hyperbaric bupivacaine 0.5% (control group) or bupivacaine combined with 45mg of clonidine (clonidine group) or with 25mg of fentanyl (fentanyl group). Study of starting time and total time of sensory and motor blockade, level of sedation, total time of perioperative analgesia, maternal hemodynamic and fetal parameters were compared.
**Results:** Time to two segment regression was increased in fentanyl group and clonidine group than in control group. Total time of analgesia was significantly more in fentanyl group and clonidine group than in control group. There was increased incidence of side-effects in clonidine group than other two groups.
**Conclusion:** Postoperative analgesia was increased by addition of 25mg fentanyl and 45mg clonidine to bupivacaine, with more side effects like hypotension, bradycardia and sedation in clonidine group.



## 1. Introduction

Lower segment caesarean section is most commonly performed surgical procedure usually done under subarachnoid block with 0.5% hyperbaric bupivacaine. It has many benefits like easy to perform, quick onset of action and good muscle relaxation. Pregnancy is affliated with difficult airway due to mucosal edema, friable mucosa, large breasts and worsening of Mallampatti Class. It helps in establishing bond between mother and baby. This gives regional anesthesia a definite advantage over general anesthesia.

Surgery on the uterus under subarachnoid block is often associated by visceral pain. Blockade to the T4 dermatome is needed to perform caesarean delivery without maternal discomfort. It is commonly related with hypotension and attendant decreased utero-placental perfusion.[1] Occurrence of hypotension can be reduced by reducing the volume of local anesthetic agent, but it carries a risk of insufficient analgesia.[2] Various adjuvants like clonidine have been used with local anesthetics in subarachnoid block to avoid intra-operative visceral and somatic pain and to lengthen postoperative analgesia.[3] Alpha-2 ($\alpha_2$) adrenergic receptor agonists like clonidine and dexmedetomidine have been the focus of interest as adjuvants to intrathecal local anesthetics due to their sedative, analgesic, perioperative sympatholytic and hemodynamic stabilizing properties.[4] Benefits of adding clonidine to intrathecal bupivacaine like quicker onset of action and better intra-operative sensory and motor blockade, lengthen post-operative analgesia and reduced dosage of local anesthetic agent have been demonstrated in various studies.[3] Clonidine has also been used intrathecally as an adjuvant with bupivacaine up to a dose of 1 $\mu$g/kg without notable maternal and neonatal side-effects.[5] Usual dose of clonidine (15-150$\mu$g) may be some

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times related with bradycardia, hypotension and sedation.[3]

Opioids are most commonly used intrathecal adjuvants. Fentanyl and Sufentanyl are the most studied and commonly used lipophilic drugs for intrathecal delivery. Fentanyl in various doses (10,20,30,40 $\mu$g) when added to spinal bupivacaine prolongs the total time of analgesia and decreases intraoperative nausea and vomiting.[6] Addition of small dose to spinal anesthesia can produce more quicker onset and better quality surgical block and lead to more swifter recovery of motor function and allow for earlier discharge.

This study is to evaluate the effects of addition of fentanyl (25 $\mu$g) or clonidine (45$\mu$g) to hyperbaric bupivacaine 0.5% for elective lower segment caesarean section (LSCS) in terms of sensory and motor block, hemodynamics, postoperative analgesia and neonatal outcome.

## 2. Aim

To study the comparison of fentanyl 25 $\mu$g and clonidine 45 $\mu$g with 0.5% hyperbaric bupivacaine 10mg intrathecally in lower segment caesarean section.

### *2.1. Primary objectives: To compare*

1. Sensory blockade with respect to onset, maximum level attained, time taken for attainment of maximum level, time taken for two segment sensory regression and total time of sensory blockade.
2. Motor blockade with respect to onset, maximum level, time taken for achievement of maximum level, quality of motor blockade and total time of motor blockade.

### *2.2. Secondary objectives*

1. Total time of analgesia.
2. Neonatal APGAR scores.
3. Sedation.
4. Haemodynamics
5. Side-effects: shivering, nausea, vomiting, itching.

## 3. Materials and Methods

### *3.1. Materials*

After ethical committee approval, 120 Patients in the age group between 18 and 30 years belonging to ASA class I and II undergoing elective lower segment cesarean section under subarachnoid block was selected. A detailed history, complete physical examination and investigations were done for all patients. Informed written consent was taken.

Sample size calculation revealed that 36 patients per group will be required to detect a proportional difference of 30% between the hypertension as side effect present in two groups, at an alpha of 0.05 with power of 80%. P values < 0.05 were considered to indicate statistical significance. So I intended to take more than 36 patients per group.

The study population of 120 patients were randomly divided into 3 equal groups of 40 in each group:

Group I: 0.5% Hyperbaric Bupivacaine 10mg (2ml) + Fentanyl 25$\mu$g (0.5ml).

Group II: 0.5% Hyperbaric Bupivacaine 10mg (2ml) + Clonidine 45 $\mu$g (0.3ml)

Group III: 0.5% Hyperbaric Bupivacaine 10mg (2ml) + 0.5ml normal saline.

### *3.2. Methodology*

The present study included 120 patients aged between 21 – 35 years classified as ASA- I/II scheduled for elective lower segment caesarean section. All patients were examined in the pre-operative period, where the entire technique along with the procedure was explained with written informed consent. Data was collected in pretested proforma meeting the objectives of the study. All the patients were investigated for Hb, TLC, platelet count, Blood sugar, B. Urea, S. Creatinine, BT, CT, Blood group, HIV, HBsAg, ECG, Urine analysis. General, systemic examinations and assessment of the airway were performed. All Patients will be fasted 8 hours for solid food and 4 hours for clear fluids. Intravenous line will be obtained with 18G cannula and will be loaded with Ringer lactate 500ml half an hour before induction of anesthesia. All patients will receive Inj. Ranitidine 50mg IV and Inj. Metoclopramide 10mg IV for aspiration prophylaxis before surgery. The patients were randomly allotted to 3 groups to receive intrathecal Fentanyl 25 $\mu$g with clonidine 45 $\mu$g with 0.5% hyperbaric bupivacaine 10mg. In the operating room, patients were monitored with electrocardiography (ECG), oxygen saturation ($SPO_2$), noninvasive blood pressure (NIBP) and pulse by using Philips monitor and pulse oximeter. Fentanyl and Clonidine were taken in tuberculin (BCG) syringe of 1ml through which only 25 $\mu$gm of Fentanyl or 45 $\mu$gm of Clonidine was administered into the 5ml syringe in which 2ml hyperbaric bupivacaine was taken. In sitting position and under all aseptic precautions subarachnoid block was performed at L2-L3 / L3-L4 level through midline approach using 23/25 G Quincke's spinal needle and study drug was injected only after confirmation of needle tip in the subarachnoid space by clear and free flow of Cerebrospinal Fluid on aspiration. The time of intrathecal injection was considered as 0. After anesthesia patient was made to lie down in the supine position immediately with the table kept flat horizontally, wedge kept under right hip and supplemental oxygen was given.

### *3.3. Inclusion criteria*

1. Patients in the age group 18 to 30 years.
2. Patients belonging to ASA Class I and II.

### 3.4. Exclusion criteria

1. Known hypersensitivity to local anesthetics or clonidine and fentanyl.
2. Patients with complications like anemia, heart disease, gestational hypertension/diabetes mellitus and hypertension.
3. Patients having absolute contraindications for spinal anesthesia like raised intracranial pressure, severe hypovolemia, bleeding diathesis, local infection.
4. Height <150 cm and >170cm.
5. BMI > 3.
6. Patient refusal.

### 3.5. The following parameters observed and recorded

Onset, maximum level of sensory blockade and motor blockade attained. Sensory blockade was tested using pinprick method every 15 seconds till the onset of sensory blockade and thereafter at 2mins intervals till the maximum level of sensory blockade is achieved. Quality of motor blockade was assessed by modified Bromage scale. The two segments sensory regression time was taken. Total duration of sensory blockade and motor blockade was noted. Total duration of analgesia was noted. Sedation score assessed every 15 minutes intra-operatively and every hourly in the postoperative period for first 6 hours using Ramsay sedation score. Neonatal APGAR scores 1 and 5 minutes were taken. Postoperative pain was assessed using Visual analogue scale every half-hourly for the first 6 hours and hourly till 24 hours and time to first rescue analgesic request were recorded.

**Table 1:** Modified bromage scale

| **Grade** | |
|---|---|
| Grade 0 | No motor paralysis |
| Grade 1 | Unable to raise extended leg |
| Grade 2 | Unable to flex knee joint |
| Grade 3 | Unable to flex ankle |
| Grade 4 | Unable to move toes |

**Table 2:** Ramsay sedation score

| **Score** | **Responsiveness** |
|---|---|
| 1 | Patient is anxious and agitated |
| 2 | Patient is co-operative, oriented and tranquil |
| 3 | Patient responds to command only |
| 4 | Patient exhibits brisk response to light glabellar tap or loud auditory stimulus |
| 5 | Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus |
| 6 | Patient exhibits no response |

Assessment of postoperative pain and pain relief is done by studying all parameters before shifting the patient to the ward. Strict instructions were written on paper. No narcotics, analgesics, sedatives to be given. Assessment of pain was done by patients themselves, or by using pin prick sensation to 23G hypodermic needle and dermatomes levels were tested every minute until the highest level had established to T6. Post-operatively, the pain was recorded by VAS. Any hypotension that is 20% fall from baseline blood pressure and side-effects like bradycardia, respiratory depression, nausea, vomiting, itching and chest tightness were noted. Any fall in MAP (Mean arterial pressure) of more than 20% of pre-induction value was treated with an I.V. bolus of vasopressor drug and by pushing the I.V. fluids. Any episode of bradycardia (HR less than 50 beats/min.) was treated with increments of 0.02mg/kg of I.V Atropine. And I.V. 75 mg diclofenac was administered as rescue analgesia when VAS score was greater than or equal to 4 whenever patients complaints of pain.

### 3.6. Data collection and methods

The following pharmaco-dynamics effects of the drugs in each group were observed and tabulated:

1. Bromage Scale
2. Visual Analog Scale
3. Pulse rate
4. Systolic & diastolic pressure
5. Mean arterial pressure
6. Respiratory rate
7. Oxygen saturation
8. Apgar score
9. Side effects like itching, sedation, nausea & vomiting.
10. Quality of sedation using Ramsay sedation score.

## 4. Discussion and Results

The current study was done to compare and evaluate the efficacy of intrathecal fentanyl and clonidine in caesarean section surgeries, conducted in department of anesthesiology of Index Medical College, Hospital and Research Centre, Indore (M.P).

In our study a total of 120 patients were randomly divided into 3 groups with 40 in each group:

1. Group I: 0.5% Hyperbaric Bupivacaine 10mg (2ml) + Fentanyl 25$\mu$g (0.5ml).
2. Group II: 0.5% Hyperbaric Bupivacaine 10mg (2ml) + Clonidine 45 $\mu$g (0.3ml).
3. Group III: 0.5% Hyperbaric Bupivacaine 10mg (2ml) + Normal Saline 0.5ml.

Bupivacaine binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. Without depolarization, no initiation or conduction of a pain signal can occur.[7,8]

It is stable and needs no special precautions for storage. It is safe, has minimal side effects, toxic

**Table 3:** Comparison of mean starting time of sensory block among various groups

| Groups | N | Onset of Sensory Block[Mean ± SD] | F Value | P Value |
|---|---|---|---|---|
| Clonidine group | 40 | 3.70 ± 1.20 | | |
| Fentanyl group | 40 | 3.03 ± 0.92 | 19.347 | 0.000* |
| Control group | 40 | 4.48 ± 0.99 | | |
| Total | 120 | 3.73 ± 1.19 | | |

**Table 4:** Comparison of meantotal time of sensory block among various groups

| Groups | N | Duration of Sensory block[Mean ± SD] | F Value | P Value |
|---|---|---|---|---|
| Clonidine group | 40 | 204.38 ± 19.86 | | |
| Fentanyl group | 40 | 269.90 ± 27.69 | 148.892 | 0.000* |
| Control group | 40 | 181.03 ± 23.44 | | |
| Total | 120 | 218.43 ± 44.59 | | |

**Table 5:** Comparison of mean starting time of motor block among various groups

| Groups | N | Onset of motor block [Mean ± SD] | F Value | P Value |
|---|---|---|---|---|
| Clonidine group | 40 | 3.15 ± 0.89 | | |
| Fentanyl group | 40 | 2.48 ± 0.59 | 29.621 | 0.000* |
| Control group | 40 | 3.88 ± 0.91 | | |
| Total | 120 | 3.17 ± 0.99 | | |

**Table 6:** Comparison oftotal time of motor block among various groups

| Groups | N | Duration of motor block [Mean ± SD] | F Value | P Value |
|---|---|---|---|---|
| Clonidine group | 40 | 417.55 ± 34.54 | | |
| Fentanyl group | 40 | 463.43 ± 55.53 | 145.091 | 0.000* |
| Control group | 40 | 308.73 ± 30.74 | | |
| Total | 120 | 396.57 ± 77.17 | | |

**Table 7:** Comparison of adverse events between the groups

| | Clonidine group (n=40) | | Fentanyl group (n=40) | | Control group (n=40) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Shivering | 3 | 7.5 | 0 | 0.0 | 11 | 27.5 |
| Nausea/Vomiting | 21 | 52.5 | 7 | 17.5 | 3 | 7.5 |
| Hypotension | 20 | 50.0 | 9 | 22.5 | 3 | 7.5 |
| Bradycardia | 7 | 17.5 | 1 | 2.5 | 5 | 12.5 |
| Pruritus | 0 | 0.0 | 7 | 17.5 | 0 | 0.0 |
| Dryness of mouth | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

**Table 8:** Comparison of sedation grades between the groups

| Sedation Grading | Clonidine group (n=40) | | Fentanyl group (n=40) | | Control group (n=40) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Grade I | 14 | 35.0 | 24 | 60.0 | 33 | 82.5 |
| Grade II | 15 | 37.5 | 16 | 40.0 | 7 | 17.5 |
| Grade III | 11 | 27.5 | 0 | 0.0 | 0 | 0.0 |
| Grade IV | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Grade V | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Grade VI | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Total | 40 | 100.0 | 40 | 100.0 | 40 | 100.0 |

reactions and neurological complications. The advantage of bupivacaine as a spinal anesthetic agent is that hyperbaric bupivacaine 0.5% provides a prolonged regional anaesthesia as compared to local anaesthesia thus avoiding need for combination of vasoconstrictor drugs.Sensory analgesia continued for much longer time than other available local anesthetic reducing an early postoperative requirement of analgesia,adequate motor and sensory blockage is achieved thus avoiding use of muscle relaxant.

A single dose of fentanyl administered IV has a quicker onset and shorter duration of action than morphine. Cardiopulmonary bypass causes clinically insignificant effects on the pharmacokinetics of fentanyl despite associated hemodilution, hypothermia, non-physiologic blood flow and cardiopulmonary bypass-induced systemic inflammatory responses.[9]

It is excreted by the kidneys and can be detected in the urine for 72 hrs after a single iv dose of fentanyl. Fentanyl is a substrate for hepatic P450 enzymes and is susceptible to drug interactions that reflect interference with enzyme activity.[10]

Clonidine is a centrally acting selective partial a2 adrenergic agonist (a2 to a1 at 220:1).[11] It Is considered to be a mixed agonist that stimulates both a1, a2 and imidazole receptors.[12] It is Lipid soluble and easily penetrates the blood brain barrier to reach the hypothalamus and medulla when injected epidurally. a-2A receptors mediate sedation, analgesia and sympatholysis, whereas a-2B receptors mediate vasoconstriction and possibly anti shivering effects. a-2C receptors may mediate the startle response. One of the highest densities of a-2 receptors is present in the pontine locus coeruleus, an important source of sympathetic nervous system activation of the forebrain and vital modulator of vigilance. Sedative effects evoked by a-2 agonists most likely reflect inhibition of this nucleus. The medullar dorsal motor complex in the brain stem has a high density of a-2 adreno-receptors. These receptors are likely to be associated with central hemodynamic effects seen with a-2 adreno- receptor agonists.[13]

In my study I found out that there is no significant difference in age group, duration of surgery and ASA status between all the three groups, hence all the groups are comparable to each other with respect to age, duration of surgery and ASA status which in-return provide us with a uniform platform to evenly compare the results obtained.

The starting time for sensory block upto $T_8$ level in clonidine group was 3.70 $\pm$ 1.20 minutes, in fentanyl group it was 3.03 $\pm$ 0.92 minutes and in control group it was 4.48 $\pm$ 0.99 minutes. The mean starting time of sensory block was maximum in control group and minimum in fentanyl group. The difference was statistically significant (P<0.05).

The total time for regression of sensory block from $T_{10}$ or below in clonidine group was 204.38 $\pm$ 19.86 minutes, in fentanyl group was 269.90 $\pm$ 27.69 minutes and in control group was 181.03 $\pm$ 23.44 minutes. The total time of sensory block was maximum in fentanyl group and minimum in control group. The difference was found to be statistically significant (P<0.05).

The starting time for motor block in clonidine group was 3.15 $\pm$ 0.89 minutes, in fentanyl group it was 2.48 $\pm$ 0.59 minutes and in control group it was 3.88 $\pm$ 0.91 minutes. The mean starting time for motor block was maximum in control group and minimum in fentanyl group. The difference was found to be statistically significant (P<0.05).

The total time for motor block in clonidine group was 417.55 $\pm$ 34.54 minutes, in fentanyl group it was 463.43 $\pm$ 55.53 minutes and in control group it was 308.73 $\pm$ 30.74 minutes. The mean total time for motor block was maximum in fentanyl group and minimum in control group. The difference was found to be statistically significant (P<0.05).

The mean time for first dose of analgesia in clonidine group was 290.33 $\pm$ 23.71 minutes, in fentanyl group it was 363.78 $\pm$ 38.13 minutes and in control group it was 201.10 $\pm$ 17.94 minutes. The mean time for first dose of analgesia was longest in fentanyl group and shortest in control group. The difference was found to be statistically significant (P<0.05).

The mean Visual Analogue Score in clonidine group was 0.13 $\pm$ 0.33, in fentanyl group was 0.05 $\pm$ 0.22 and in control group was 0.45 $\pm$ 0.59. The mean Visual Analogue Score was maximum in control group and minimum in fentanyl group. The difference was found to be statistically significant (P<0.05).

In APGAR score comparison there was no statistically or clinically significant difference among all the comparing groups.

In clonidine group, shivering was seen in 3 (7.5%) patients, in 21 (52.5%) patients nausea/vomiting was seen, in 20 (50.0%) patients hypotension was seen and in 7 (17.5%) patients bradycardia was seen. In fentanyl group, in 7 (17.5%) patients nausea/vomiting was seen, in 9 (22.5) patients hypotension was seen and in 1 (2.5%) patient bradycardia was seen. In control group, shivering was seen in 11 (27.5%) patients, in 3 (7.5%) patients nausea/vomiting was seen, in 3 (7.5%) patients hypotension was seen and in 5 (12.5%) patients bradycardia was seen. Shivering was present highest in control group, followed by clonidine group. Nausea/Vomiting, hypotension were highest in clonidine, followed by fentanyl and minimum in control group. Bradycardia was highest in clonidine, then control and minimum in the fentanyl group.

In all the three groups, Sedation grading I to III only were seen. The association between the sedation score and the groups was found to be statistically significant (P<0.05). Grade III sedation was seen only in the clonidine group. Grade I sedation score was only seen in control and fentanyl groups.

The heart rate was comparable between the groups at pre, 2 minutes, 4 minutes, 6 minutes, 8 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 50 minutes and 60 minutes (P>0.05), showing that heart rate was comparable between the three groups at these time intervals. Heart rate was statistically significant at post (P<0.05), with maximum heart rate in control group, followed by clonidine group and minimum in the fentanyl group.

## 5. Financial Implications

The patients are managed according to the protocol of the institution laid down for the management of the patient. All the charges as per institution norms will be borne by the patient. All study related expenditures were borne by the investigator himself.

## 6. Ethical and Legal Considerations

The protocol of the present study was submitted to the ethics committee of Index Medical College, Hospital & Research Center, Indore. After getting there due approval, the study was initiated in the institute. A patient information and consent was given to the patients in their local language, all their queries were satisfactorily answered and when they were willing to participate, signature of the patient or her husband/guardian was obtained and only after that study was initiated.

## 7. Conclusion

It is concluded from the present study that the addition of 45 mg of clonidine and 25 mg fentanyl to bupivacaine improves the onset and total time of sensory block and motor block with relative hemodynamic stability, prolongs the total time of analgesia and reduces the need of analgesics in comparison to bupivacaine alone. However, prolongation of perioperative analgesia was more with fentanyl compared to clonidine. Clonidine also had unwanted side effects like nausea/vomiting, hypotension, bradycardia and sedation. Hence, I suggest that addition of fentanyl is excellent additive to bupivacaine as it increases the quality of anesthesia and increases the duration of analgesia without any harmful effects on mother or baby.

## 8. Source of Funding

None.

## 9. Conflict of Interest

None.

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