

## Study of Clonidine vs Fentanyl Intrathecally with 0.5% Bupivacaine in Vaginal Hysterectomy: A Comparative Study

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### Abstract

Bupivacaine is the most common drug used in spinal anesthesia in vaginal hysterectomy which gives adequate anesthesia for the procedure. Clonidine is  $\alpha_2$  agonist used to prolong the duration of intrathecally administered local anesthetic and has potent antinociceptive properties. Fentanyl not only improves the quality of intra-operative analgesia but also reduces the need of supplemental sedation. In the present study, we tried to find out whether quality of anesthesia is better with low dose bupivacaine and clonidine or with low dose bupivacaine and fentanyl. *Methods:* Prospective, randomised double-blind, controlled study was conducted in a tertiary care institution. 80 patients ASA Grade I and II scheduled for vaginal hysterectomy were randomly allocated into two groups by using computer generated random numbers. Group BC (n = 40) received 0.5% Hyperbaric bupivacaine 2.8 ml (14 mg) + 25 mcg Clonidine and Group BF (n = 40) received 0.5% hyperbaric bupivacaine 2.8 ml (14 mg) + 30 mcg Fentanyl intrathecally. Time for onset of sensory and motor blockade, time to achieve maximum sensory and motor blockade, time for segment regression up to L1, side effects, peri-operative and post-operative analgesic requirements were assessed. *Results:* Mean duration of onset to peak sensory block ( $5.45 \pm 0.50$  min), onset to peak motor block ( $7.05 \pm 0.22$  min) was significantly higher in group BC as compared to group BF ( $6.90 \pm 0.38$  min) and ( $8.67 \pm 0.47$  min) respectively. Significant difference in mean duration of sensory block and motor block ( $189.80 \pm 6.49$  min,  $247.28 \pm 8.42$  min) in group BC and group BF ( $150.23 \pm 4.23$ ,  $197.08 \pm 6.25$  min) were noted. Duration of post-operative analgesia was significantly higher in group BC ( $495.93 \pm 22.43$  min) as compared to group BF ( $269.33 \pm 17.98$  min). There was significant difference between VAS score in group BC and group BF except 4th hr and 18th hr. All patients were hemodynamically stable and no significant difference in post-operative sedation and adverse effects was observed. *Conclusion:* Clonidine and fentanyl are good adjuvant drugs and their use intrathecally as an additive to bupivacaine extends the duration of spinal anesthesia significantly, lowering the need to administer general anesthesia if duration of surgery is prolonged. Further they also provides excellent post-operative analgesia. Clonidine is better adjuvant with bupivacaine in view of better sensory and motor blockade, prolonged post-operative analgesia.

**Keywords:** Clonidine; Fentanyl; Analgesia; Vaginal hysterectomy.

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## Introduction

Pain, one of the most dramatic, complex and universal phenomenon is defined as “unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Post-operative pain is associated with various systemic adverse responses all contributing to increase post-operative morbidity and mortality. Hence, an effective pain relief after surgery is essential for optimal care of surgical patients. Effective post-operative pain is an essential component of the care of the patient. Inadequate pain control, apart from being in human may result in increased morbidity and mortality.<sup>1</sup> Good analgesia can reduce deleterious effects. Afferent neural blockade with local anesthetics is the most effective analgesic technique. Next in order of effectiveness are high dose opioid therapy and NSAIDS.

Regional anesthesia avoids the complications of general anesthesia and also intubation while providing adequate analgesia and muscle relaxation in the operative area. It thus is a good alternative to general anesthesia. It also provides post-operative pain relief. Spinal anesthesia is a simple technique with rapid onset of action most commonly used in vaginal hysterectomy.<sup>2</sup> Most common Local anesthetic used for spinal anesthesia is bupivacaine, but due to short duration of action early analgesic intervention in the post-operative period is required.<sup>3</sup> A number of adjuvants to local anesthetics have been used intrathecally to prolong the intra-operative and post-operative analgesia. The addition of low doses of fentanyl and clonidine to local anesthetics during spinal anesthesia decreases the incidence of local anesthetic related side effects, reduces the time of onset of the sensory and motor blockade, and increases the quality of intra and post-operative analgesia by reducing the dose of local anesthetics.<sup>4</sup> Clonidine is a selective partial agonist for  $\alpha_2$ -adrenoreceptor, with ratio of approximately 200:1 ( $\alpha_2:\alpha_1$ ),<sup>5</sup> it has potent antinociceptive properties<sup>6</sup> and increases the duration of analgesia. Fentanyl is a synthetic opioid and  $\mu$  receptor agonist, about 100 times more potent than morphine as an analgesic.<sup>7</sup> It is most commonly administered intravenously, although it is also commonly administered epidurally and intrathecally for acute post-operative and chronic pain management. Fentanyl not only improves the quality of intra-operative analgesia but also reduces the need of supplemental sedation.<sup>8</sup> In the present study, we tried to find out whether quality of anesthesia is better with low dose bupivacaine

and clonidine or with low dose bupivacaine and fentanyl.

## Aims and Objectives

Aim of our study was to evaluate the effectiveness of 0.5% bupivacaine with clonidine and 0.5% bupivacaine with fentanyl for spinal anesthesia in terms of—

- Onset and duration of sensory blockade;
- Onset and duration of motor blockade;
- Duration of post-operative sedation;
- Duration of post-operative analgesia;
- Complications, if any.

## Materials and Methods

### Study Design

After obtaining institutional and ethical committee approval, written informed consent was taken from all patients prior to joining the study. Study was a prospective, randomised double-blind, controlled, single centre study. 80 patients ASA grade I and ASA grade II scheduled for vaginal hysterectomy were randomly allocated into two groups by using computer generated random numbers.

### Inclusion Criteria

ASA Grade I and II patients posted for vaginal hysterectomy, aged between 45 and 65 years, normotensive patients.

### Exclusion Criteria

ASA Grade III and IV patients, patients with significant cardiovascular, renal, hepatic dysfunction, having contraindication for spinal anesthesia and morbidly obese patients.

### Blinding

The drug solution to be used for spinal anesthesia was prepared by another anesthetist according to the randomization chart. The randomization code was sealed in an envelope. The code number of each individual was also sealed in the envelope.

### Sample size

Sample size is calculated by using the pilot study of 25 patients with parameter duration of motor block

in minutes. Group BC = Mean ± SD is 198.6 ± 43.6 min and Group BF = Mean ± SD is 174 ± 15.8 min. By using formula:

$$\frac{2Z\alpha + Z_{(1-\beta)}}{d^2} \times (SD)^2 \text{ combined}$$

$$Z\alpha = 1.96, Z_{1-\beta} = 0.84;$$

$$\text{Combined SD} = 38.39;$$

$$\text{Difference of means (d)} = 24.3;$$

Minimum required sample size (n) = 39.13 ≈ 40 per group. **Group BC (n = 40):** Patients received 0.5% Hyperbaric bupivacaine 2.8 ml (14 mg) + 25 mcg Clonidine; **Group BF (n = 40):** Patients received 0.5% hyperbaric bupivacaine 2.8 ml (14 mg) + 30 mcg Fentanyl.

### Study plan

Pre-anesthetic evaluation was carried out in detail which included general examination, systemic examination, airway assessment, spine and neck examination. All baseline investigations were done including hemoglobin, platelet count, bleeding time, clotting time, blood sugar level, liver function tests, renal functions tests, serum electrolytes, ECG and chest X-ray PA view. Group BC (n = 40) received 0.5% Hyperbaric Bupivacaine 2.8 ml (14 mg) + 25 mcg Clonidine and group BF (n = 40) received 0.5% Hyperbaric Bupivacaine 2.8 ml (14 mg) + 30 mcg Fentanyl intrathecally. Pre-operatively pulse rate, blood pressure, oxygen saturation were noted. After shifting the patient on operating table monitors like ECG, NIBP, pulse oxymeter were attached. Intravenous canula of 18 G was secured and pre-loading done with 10 ml/kg of Ringer lactate solution and pre-medicated with inj. Ondansetron 0.08 mg/kg I.V. and inj. Ranitidine 1 mg/kg I.V. before giving spinal anesthesia. Painting and draping done in sitting position under all aseptic conditions. After palpating L3-L4 space subarachnoid block was given in Group BC patients with 0.5% Hyperbaric Bupivacaine 2.8 ml (14 mg) + 25 mcg Clonidine and in Group BF patients with 0.5% Hyperbaric Bupivacaine 2.8 ml (14 mg) + 30 mcg Fentanyl with 25 G spinal needle. Supine position was given immediately. All patients were given supplemental oxygen by venti mask @4–6 lit/min.

### Intra-operative monitoring

Intra-operatively pulse rate, blood pressure, O<sub>2</sub> saturation, ECG was monitored, Sensory block was assessed by a pin prick test performed with 22 G short bore needle. Motor block was assessed using

by using Bromage score:

Bromage 0	Patient is able to move hip, knee and ankle
Bromage 1	Patient unable to move hip but able to move knee and ankle
Bromage 2	Patient unable to move hip and knee but able to move ankle
Bromage 3	Patient unable to move hip, knee and ankle

After intrathecal drug injection, intra-operatively data was recorded during 1<sup>st</sup> 2 hours at 5,15, 30, 45, 60,90,120 minutes. During surgery, patient did not receive any sedation.

### Post-operative monitoring

Assesment of post-operative sedation done by using Ramsay sedation scale.

Score	Level of sedation
1	Anxious or agitated or restless or both
2	Co-operative, oriented and tranquil
3	Responding to commands only
4	Brisk response to light glabellar tap
5	Sluggish response to light glabellar tap
6	No response to light glabellar tap

Assesment of post-operative analgesia done by using Visual Analogue Scale between 0 and 10. 0-No pain: 10-most severe pain. Post-operatively data was recorded for first 4 hour every hourly, for next 8 hours every 2 hourly, for next 12 hours every 6 hourly interval upto 24 hours. Duration of Anesthesia was measured as time interval from intrathecal injection to regression of sensory block below L1.

### Monitoring and treatment of side effects

Intra-operative and post-operative side effects such as nausea, vomiting, hypotension, bradycardia, shivering and sedation were noted till complete recovery. Hypotension was defined as a decrease in systolic blood pressure more than 30% of baseline value. Hypotension was treated with oxygen supplementation, I.V. fluids or Mephenterine. Bradycardia (Pulse rate < 60) treated with inj. Atropine. Inj Ondansetron 0.08 mg/kg used for nausea and vomiting. Inj. Naloxone was kept ready for respiratory depression.

### Statistical analysis

Statistical evaluation was done by using 2 independent sample t-test and Mann-Whitney U-test. The detailed data was entered into well tabulated Microsoft Excel sheet and subsequently

analyzed statistically. Graphical display was done for visual inspection, *p* - value less than 0.05 was considered to be significant.

**Results**

There was no statistical difference among groups as far as age, weight, height, and duration of surgery concerned. Mean duration of onset to peak sensory block ( $5.45 \pm 0.50 \text{ min}$ ), onset to peak motor block ( $7.05 \pm 0.22 \text{ min}$ ) was significantly higher in Group BC as compared to Group BF ( $6.90 \pm 0.38 \text{ min}$ ) and ( $8.67 \pm 0.47 \text{ min}$ ) respectively. Significant difference in mean duration of sensory block and motor block ( $189.80 \pm 6.49 \text{ min}$ ,  $247.28 \pm 8.42 \text{ min}$ ) in Group BC and Group BF ( $150.23 \pm 4.23$ ,  $197.08 \pm 6.25 \text{ min}$ ) were noted. Duration of post-operative analgesia was significantly higher in group BC ( $495.93 \pm 22.43 \text{ min}$ ) as compared to group BF ( $269.33 \pm 17.98 \text{ min}$ ). There was significant difference between VAS score in group BC and group BF except 4<sup>th</sup> hr and 18<sup>th</sup> hr. All patients were hemodynamically stable and no significant difference in post-operative sedation and adverse effects was observed, (Tables 1-4 are showed & Figs. 1-3 are displayed).

**Table 1:** Onset to peak sensory and complete motor block duration

	Group BC (n = 40)		Group BF (n = 40)		p - value
	Mean	SD	Mean	SD	
Onset to peak sensory block	5.45	0.50	6.90	0.38	< 0.001
Onset to motor block (Grade IV)	7.05	0.22	8.68	0.47	< 0.001

\*Significant

By using 2 independent sample *t*-test *p* - value < 0.05 therefore, there is significant difference between mean onset of sensory block and onset of motor block in Group BC and Group BF.

**Table 2:** Mean duration of sensory and motor block

	Group BC (n = 40)		Group BF (n = 40)		p - value
	Mean	SD	Mean	SD	
Duration of sensory block	189.80	6.49	150.23	4.23	< 0.001*
Duration of motor block	247.28	8.42	197.08	6.25	< 0.001*

\*Significant

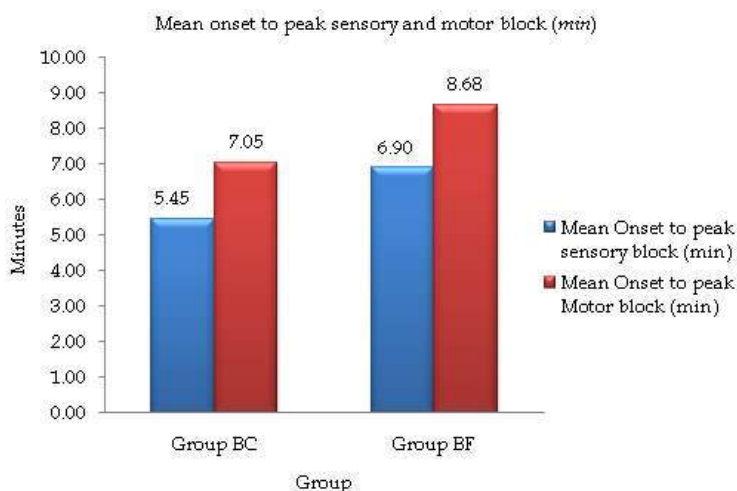
By using 2 independent sample *t*-test *p* - value < 0.05 therefore, there is significant difference between mean duration of sensory block and motor block in Group BC and Group BF.

**Table 3:** Mean duration of analgesia

Group	Number of patients	Duration of Analgesia (min)		p - value
		Mean	SD	
Group BC	40	495.93	22.43	< 0.001*
Group BF	40	269.33	17.98	

\*Significant

By using 2 independent sample *t*-test *p* - value < 0.05 therefore, there is significant difference between mean duration of analgesia (*min*) in Group BC and Group BF.



**Fig. 1:** Onset to peak sensory and complete motor block duration

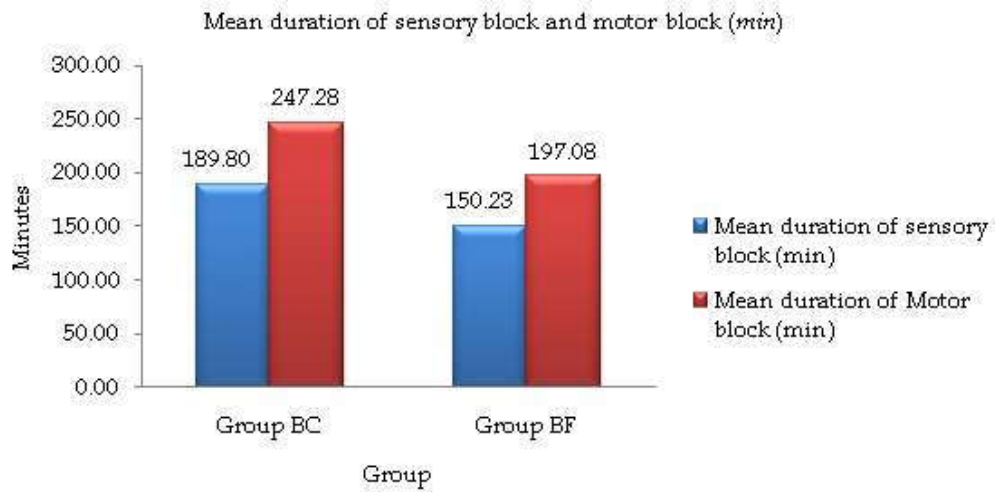


Fig. 2: Mean duration of sensory and motor block

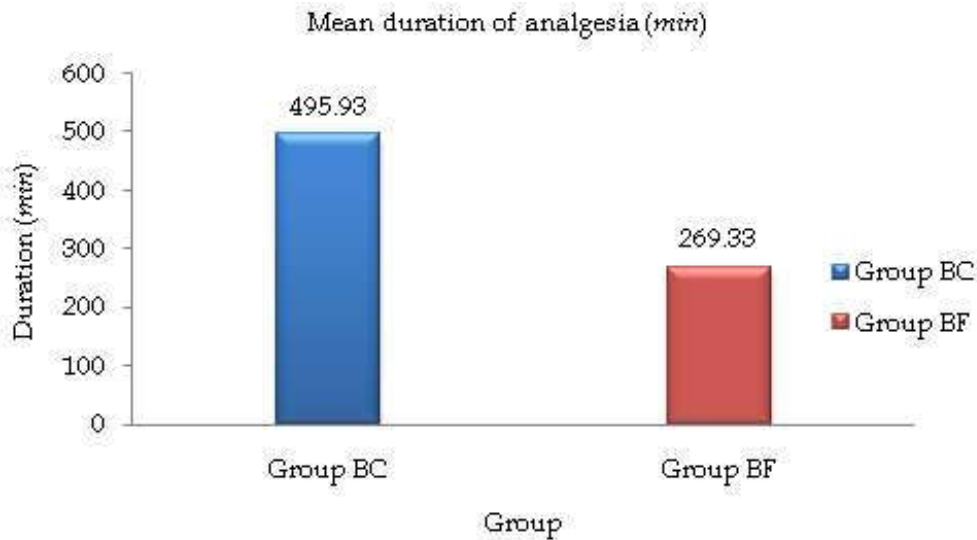


Fig. 3: Mean duration of analgesia

Table 4: Mean visual analogue scale

VAS at	VAS						p - value
	Group BC			Group BF			
	Min.	Max.	Median	Min.	Max.	Median	
1 hr	0	0	0	0	2	0	0.043*
2 hr	0	0	0	1	5	2	< 0.001*
3 hr	0	0	0	0	6	5	< 0.001*
4 hr	0	0	0	0	5	0	0.079
6 hr	1	5	2	0	3	1	< 0.001*
8 hr	0	6	5	2	6	3	< 0.001*
10 hr	1	2	1	0	6	5	< 0.001*
12 hr	2	5	2	0	4	0	< 0.001*
18 hr	2	6	5	5	6	5	0.876
24 hr	2	6	2	2	5	3	< 0.001*

\*Significant

By using Mann-Whitney *U*-test *p* - value < 0.05 therefore there is significant difference between VAS score in Group BC and Group BF except 4<sup>th</sup> hr and 18<sup>th</sup> hr.

## Discussion

Local anesthetics are commonest agents used for spinal anesthesia, but due to their relatively short duration of action, post-operative period needs the early analgesic intervention.<sup>9</sup> Clonidine is selective partial agonist for  $\alpha_2$  adrenoreceptors.<sup>10</sup> The analgesic effect following its intrathecal administration is mediated spinally through activation of post synaptic  $\alpha_2$  receptors in substantia gelatinosa of spinal cord. It works by blocking the conduction of C and A $\delta$  fibers.<sup>11</sup> It also increases potassium conductance in isolated neurons *in vitro* and intensifies conduction block of local anesthetics. Fentanyl is a potent synthetic opioid analgesic with rapid onset of action.<sup>12</sup> It binds to  $\mu$ -opioid G-protein coupled receptor, which inhibit pain neurotransmitter release by decreasing intracellular calcium levels.

Addition of fentanyl or clonidine to bupivacaine may help in increasing the duration of sensory and motor blockade, post-operative analgesia and decrease the dose of local anesthetic. In this present study there was no statistical difference among groups in age, height, weight and duration of surgery.

In our study, we observed the significant difference between mean Systolic Blood Pressure (SBP) in Group BC and Group BF at 15 min to 45 min. (*p* < 0.05) and significant difference between mean Diastolic Blood Pressure (DBP) in Group BC and Group BF at 15 min, 30 min and at 60 min (*p* < 0.05). Our results were comparable with study conducted by Agarwal D *et al.*<sup>13</sup> for SBP. There is no significant difference between mean pulse rate in Group BC and Group BF at pre-operative to 120 min, (*p* > 0.05).

We found that the duration of sensory blockade was 189.80  $\pm$  6.49 min and the duration of motor blockade was 247.28  $\pm$  8.42 min in patient receiving clonidine with bupivacaine. Sethi BS<sup>11</sup> *et al.* has also shown the comparable results in which the duration of sensory blockade was 218 min (150–240 min) and duration of motor blockade was 205 (90–300 min) in patient receiving clonidine (1 mcg/kg) with bupivacaine.

Similarly the duration of analgesia was 495.93  $\pm$  22.43 min in patients receiving clonidine with bupivacaine. Shah BB<sup>4</sup> *et al.* found the similar

results where the duration of analgesia in clonidine (30 mcg) Group was 436.65  $\pm$  149.84 min.

In our study, we observed that the time to reach peak sensory level was 6.90  $\pm$  0.38 min, duration of sensory block was 150.23  $\pm$  4.23 min and the duration post-operative analgesia was 269.33  $\pm$  17.98 min in Group BF. Our findings were similar to the study conducted by Dhumal PR<sup>14</sup> *et al.* where the time to reach peak sensory level was 5.03  $\pm$  1.45 min, duration of sensory block was 121.3  $\pm$  11.4 min and the duration of post-operative analgesia was 225.3  $\pm$  29.2 min in patients receiving fentanyl (25 mcg) with bupivacaine. Another study conducted by Gauchan S<sup>15</sup> *et al.* has also revealed the comparable result for peak sensory level where the time to achieve peak sensory level was 6  $\pm$  2.5 min with 20 mcg fentanyl.

The time to reach peak sensory level was 5.45  $\pm$  0.50 min and the duration of motor block was 197.07  $\pm$  6.24 min in Group BF. Our results were comparable with the study conducted by Sanchan P<sup>16</sup> *et al.* in which they found that the time to reach peak sensory blockade was 4.43  $\pm$  0.26 min and the duration of motor block was 189.50  $\pm$  16.31 min with 75 mcg of clonidine.

Besides, the duration of sensory block was 189.80  $\pm$  6.49 min and time for first analgesic request was 495.93  $\pm$  22.43 min in Group BC. Khezri MB<sup>12</sup> *et al.* found similar results where the mean duration of sensory block was 169.66  $\pm$  25.69 min and time for first rescue analgesic was 519.44  $\pm$  86.25 min in patients receiving clonidine (75 mcg) with bupivacaine.

In our study, the mean duration of motor block was 247.28  $\pm$  8.42 min and the duration of post-operative analgesia was 495.93  $\pm$  22.43 min in Group BC. Singh RB<sup>17</sup> *et al.* found that the mean duration of motor block was 280.80  $\pm$  66.88 min and the duration of post-operative analgesia was 510.6  $\pm$  133.64 min in patients receiving clonidine (50 mcg) with bupivacaine.

The duration of sensory block was 189.8  $\pm$  6.49 min and 150.22  $\pm$  4.22 min and the duration of motor block was 247.27  $\pm$  8.42 min, 197.07  $\pm$  6.24 min in BC and BF Group respectively. Number of diclofenac injections used in BC Group was 2 & 3 (median 2) and it was 3 & 4 (median 3) in BF Group. Chopra P<sup>5</sup> *et al.* found the comparable results where the duration of sensory block was 177.8  $\pm$  43.8 min and it was 142.2  $\pm$  14.7 min in patients receiving clonidine (30 mcg) and fentanyl (15 mcg) respectively. The duration of motor block in clonidine Group was 206.6  $\pm$  43.6 min and it was 166.2  $\pm$  15.8 min in fentanyl Group. Number of diclofenac injections used in clonidine Group was 1.16(1 & 2) and it was 2.66G (2 & 3) in fentanyl group.

We found that the mean time to reach peak sensory level was  $5.45 \pm 0.50$  min in Group BC and it was  $7.05 \pm 0.22$  min in Group BF. Bhattacharjee A<sup>7</sup> *et al.* found that the mean time to reach peak sensory level in clonidine (75 mcg) Group was  $6.25 \pm 2.13$  min and it was  $6.46 \pm 3.29$  min fentanyl (25 mcg) group.

Besides, the time to reach peak sensory level was  $6.902 \pm 0.38$  min, time of regression of motor block to Bromage scale 0 was  $197.07 \pm 6.24$  min and mean duration of analgesia was  $269.32 \pm 17.98$  min in Group BF. Bacha UQ<sup>18</sup> *et al.* has also shown the similar results in which the time to reach peak sensory level was  $7.4 \pm 0.756$  min and time of regression of motor block to Bromage scale 0 was  $188.1 \pm 6.22$  min and mean duration of analgesia was  $256.1 \pm 21.328$  min with 2.5 ml bupivacaine + 25 mcg of fentanyl.

In Our study, the mean duration of sensory block was  $189.8 \pm 6.49$  min and mean sedation score was 2 in Group BC. We observed hypotension in 1 patient and bradycardia in 2 patients. Baj B<sup>9</sup> *et al.* found similar results where the mean duration of sensory block was  $192.50 \pm 31.39$  min and mean sedation score by using Ramsay sedation score was  $2.03 \pm 0.414$  min with 25 mcg of clonidine. They also noted hypotension in 2 patients and bradycardia in 3 patients.

## Conclusion

To conclude, 30 mcg clonidine and 25 mcg fentanyl is an attractive alternative as an adjuvant to spinal bupivacaine in surgical procedures of prolonged duration with minimal side effects and excellent quality of spinal analgesia. Clonidine when compared with Fentanyl, offers a better effect owing to earlier onset and prolonged duration of sensory and motor blockade as well as longer duration of post-operative analgesia.

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