

## COMPARATIVE STUDY BETWEEN BUPIVACAINE ALONE AND BUPIVACAINE WITH FENTANYL IN AXILLARY PLEXUS BLOCK FOR UPPER LIMB SURGERIES

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### ABSTRACT

#### BACKGROUND

The addition of adjuncts like Neostigmine, opioids, midazolam, dexmedetomidine, hyaluronidase, clonidine etc., to local anaesthetics for brachial plexus block may enhance the quality and duration of analgesia. Fentanyl, a phenylpiperidine derivative, is known to produce antinociception and enhance the effect of local anaesthetics when given epidurally or intrathecally. The purpose of the present study is to assess the effect of fentanyl added to brachial plexus block by axillary approach.

#### MATERIALS AND METHODS

A prospective, randomized, single blinded study was conducted on 100 patients of either sex, belonging to 15-55 years of age. ASA grade I and II admitted to Osmania General Hospital for upper limb surgeries from 2015-2017 were operated under axillary approach of brachial plexus block.

Patients were randomly divided into two groups. Patients in Group B (n = 50) were administered 40 ml of 0.25% Bupivacaine and Group BF (n = 50) were given 40mL of 0.25% Bupivacaine with preservative free fentanyl 2.5 µg/ml. The onset time and duration of sensory and motor blockade were recorded. Haemodynamic variables (i.e., heart rate, blood pressure and oxygen saturation), sedation scores and rescue analgesic requirements were recorded for 24 hrs. postoperatively.

#### RESULTS

The duration of sensory and motor block was significantly longer in Group BF compared to Group B (p <0.05), however onset of sensory and motor block was significantly prolonged in group BF compared to group B (p <0.05). Rescue analgesic requirements were significantly less in Group BF compared to Group B (p <0.05). Haemodynamics and sedation scores did not differ between the two groups in the post-operative period.

#### CONCLUSION

Fentanyl (2.5 µg/ml) in combination with 40mL of Bupivacaine (0.25%) caused significant prolongation of duration of sensory and motor block (p<0.05) but delayed the onset of both sensory and motor blockade compared to bupivacaine alone and reduced requirements for rescue analgesics and improved postoperative analgesia when used in brachial plexus block, without producing any adverse events.

#### KEYWORDS

Bupivacaine, Fentanyl, Axillary approach brachial plexus block.

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#### BACKGROUND

Brachial plexus block provides a useful alternative to general anaesthesia for upper limb surgeries. They achieve near-ideal operating conditions by producing complete muscular relaxation, maintaining stable intra-operative

haemodynamics and the risk associated with general anaesthesia are avoided. Of various local anaesthetics, Bupivacaine is used most frequently, as it has a long duration of action varying from 3 to 8 hours. Various drugs like Neostigmine, Opioids, Hyaluronidase, and Clonidine etc.,<sup>1-4</sup> have been added to local anaesthetics in order to modify the block in terms of quick onset, good quality, prolonged duration and post-operative analgesia.

Fentanyl is an opioid analgesic is known to produce antinociception and to enhance the effect of local anaesthetics when given epidurally or intrathecally. Fentanyl produces this effect by action on opioid receptors. So the present study is being undertaken in a randomized single blinded manner to evaluate the onset time and analgesic efficacy of fentanyl- Bupivacaine<sup>5,6,7,8,9</sup>

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combination compared to plain Bupivacaine for brachial plexus block by axillary approach.

**Objectives**

The present study is undertaken to compare the effectiveness of adding fentanyl (2.5µg/ml) to Bupivacaine (0.25%) to axillary approach technique of brachial plexus block for upper limb surgeries with plain Bupivacaine (0.25%).

**Following Parameters are Studied-**

1. Onset of sensory and motor blockade.
2. Duration of sensory and motor blockade.
3. Sedation score, intra and post-operatively.
4. Haemodynamic variables (HR, BP, O<sub>2</sub> saturation).
5. Number of rescue analgesics given in post-operative period

**MATERIALS AND METHODS**

This study was conducted on 100 patients undergoing upper limb surgeries aged between 15 to 55 years under brachial plexus block, axillary approach in Osmania General Hospital, attached to Osmania Medical College, Hyderabad between November 2015 and October 2017. With the permission from the hospital ethics committee and after taking the informed written consent from the patients the study was conducted.

**Inclusion Criteria**

- ASA CLASS I & II
- Aged between 15 to 55 years.
- Systolic Blood Pressure → 100 – 139 mm of Hg.
- Diastolic Blood Pressure → 60 – 89 mm of Hg.

**Exclusion Criteria**

- Patient refusal, hypersensitivity to drugs, coagulation disorders, septicaemia and local infection at the block site.

**Investigations**

- Haemoglobin, Total Leucocyte Count, Differential Leucocyte Count, Bleeding Time, Clotting Time, Random blood sugar, Urea, S. Creatinine,

**Culebras et al<sup>4</sup> Sedation Score Evaluation**

- awake and alert.
- sedated, responding to verbal stimulus.
- sedated, responding to mild physical stimulus.
- sedated, responding to moderate or severe physical stimulus.
- not arousable.

**Monitoring**

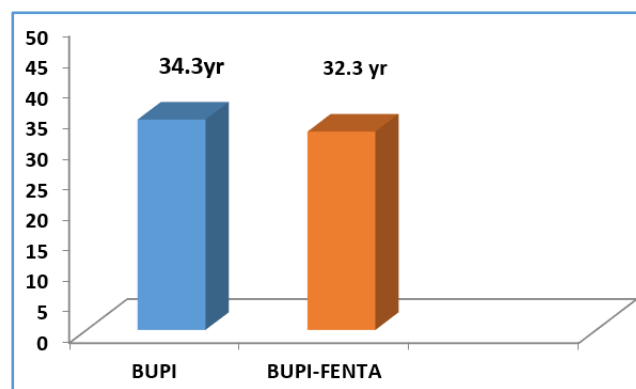
- Heart rate, non-invasive blood pressure and O<sub>2</sub> saturation were monitored.
- Duration of sensory block (the time elapsed between injection of drug and appearance of pain requiring analgesia) at 15 min interval and duration of motor

block (the time elapsed between injection of drug and complete return of muscle power) at 15 min interval were recorded.

- IM injection of Diclofenac sodium was given as rescue analgesic when patient complains of pain.
- Number of rescue analgesics needed in 24 hours of post-operative period were recorded.
- Quantitative data was analysed by student's 't' test.
- Qualitative data was analysed by Chi-square test.
- A p value of <0.05 was considered statistically significant.

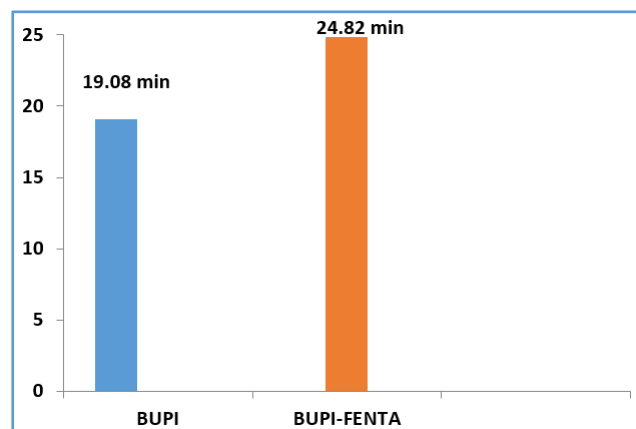
**RESULTS**

Hundred ASA Gr I and II of either sex aged between 15-55 years, posted for upper limb surgeries under brachial plexus block axillary plexus approach were selected for the study. The study was undertaken to evaluate the efficacy of Fentanyl (2.5 µg/ml) as an adjuvant to Bupivacaine (0.25%) in comparison with plain Bupivacaine (0.25%) for brachial plexus block by axillary approach.



**Graph 1. Age Distribution of Study Groups**

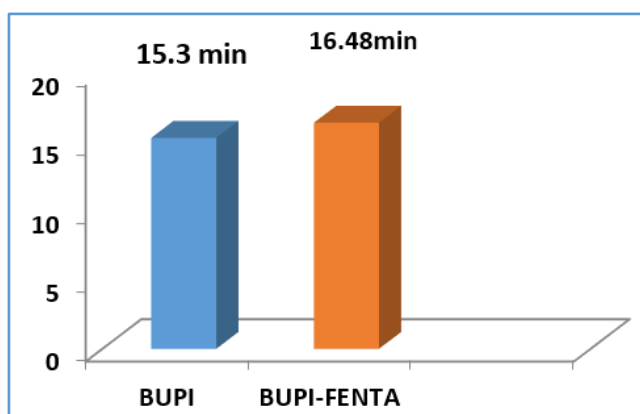
The minimum age of the patient was 15 years and the maximum age was 55 years. The mean age of the patients in group BF was 32.3 ± 10.51 and in group B was 34.3 ± 11.89 years. Age distribution between two groups were comparable.



**Graph 2. Time for Onset of Sensory Block (Min)**

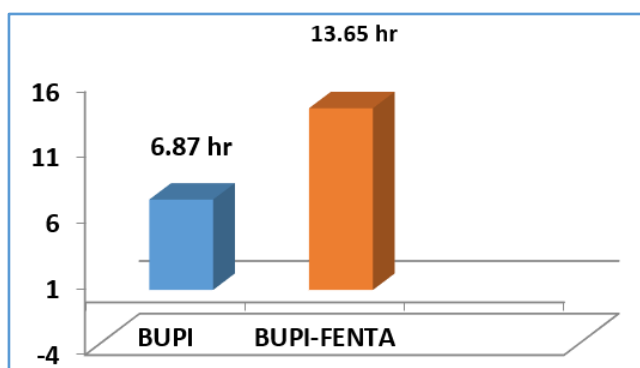
The mean time for onset of sensory block in group BF was 24.82 ± 1.66 min and in group B was 19.08 ± 1.7 min. The statistical analysis by student's unpaired 't' test showed

that, the time for onset of sensory block in group BF was significantly slower when compared to group B ( $p < 0.05$ ).



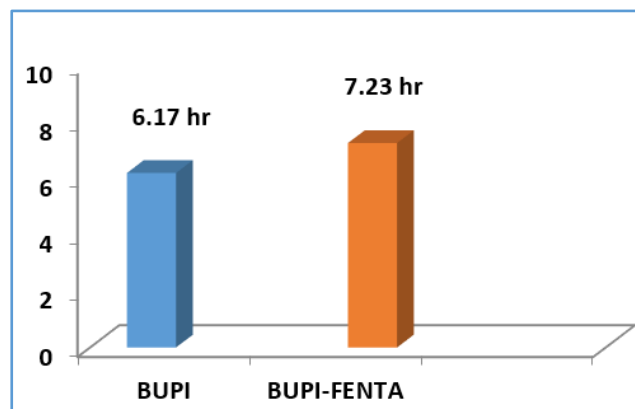
**Graph 3. Time for Onset of Motor Block**

The mean time for onset of motor block in group BF was  $16.48 \pm 2.62$  min and in group B was  $15.3 \pm 2.09$  min. The statistical analysis by unpaired student's 't' test showed that, the time for onset of motor block in group BF was significantly slower when compared to group B ( $p < 0.05$ ).



**Graph 4. Duration of Sensory Block**

Patients of both groups were observed for 24 hours. Time was noted when the patient asked for rescue analgesics. The mean duration of sensory block in group BF was  $13.65 \pm 2.01$  hours and in group B was  $6.87 \pm 0.89$  hours. The statistical analysis by students unpaired 't' test showed that the duration of sensory block in group BF was significantly longer when compared to group B ( $p < 0.05$ ).

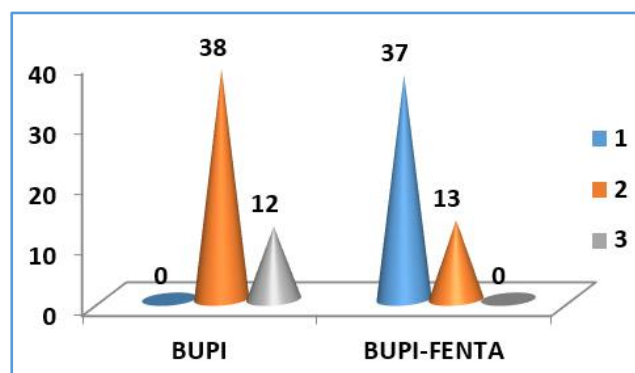


**Graph 5. Duration of Motor Block**

The mean duration of motor block in group BF was  $7.23 \pm 1.01$  hours and the group B was  $6.17 \pm 0.77$  hours. The statistical analysis by students 't' test shows significant difference, with p value less than 0.05 ( $p < 0.05$ ).

**Number of rescue analgesics in post-op 24 hours**

In group BF, 74% patients required only 1 rescue analgesic dosage and 26% of patients required 2 rescue analgesic doses in post-op 24 hours. In group B 76% of patients required 2 and 24% of patients required 3 rescue analgesic doses in post-op 24 hours. This difference in number of rescue analgesic doses required by patient of both groups is statistically significant by chi-square test ( $\chi^2 = 61.25$ ,  $P < 0.05$ ).



**Graph 6 Number of Rescue Analgesics Needed**

Time of Assessment	Scores *	Bupivacaine	Bupivacaine - Fentanyl	X2 Value, Significance
0 min	1	50 (100)	50 (100)	-
	2	0	0	No Difference
5 min	1	50 (100)	50 (100)	-
	2	0	0	No Difference
15 min	1	50 (100)	40 (80)	$X^2 = 9.0$
	2	0	10 (20)	$P < 0.05$ Sig
30 min	1	50 (100)	34 (68)	$X^2 = 16.74$
	2	0	16 (32)	$P < 0.05$ Sig
60 min	1	50 (100)	37 (74)	$X^2 = 12.73$
	2	0	13 (26)	$P < 0.05$ Sig
2 hrs	1	50 (100)	50 (100)	-
	2	0	0	No Difference

6 hrs	1	50 (100)	50 (100)	-
	2	0	0	No Difference
12 hrs	1	50 (100)	50 (100)	-
	2	0	0	No Difference
24 hrs	1	50 (100)	50 (100)	-
	2	0	0	No Difference

**Table 1. Sedation Score**

- Aware and alert.
- Sedated responding to verbal stimulus.
- Sedated, responding to mild physical stimulus.
- Sedated, respond to moderate to severe physical stimulus.
- Not arousable.

In group B, all patients were awake and alert and had sedation score of 1. In group BF, sedation corresponding to score 2 was observed in some patients between 15 min from time of injection and 60 min. 20% of patients at 15 min, 32% of patients at 30 min and 26% of patients at 60 min had sedation score of 2. None of the patients had sedation score of 3 and above during the study period. Statistical analysis of sedation score by chi-square test showed that the difference in sedation score was significant (P <0.05).

**Haemodynamic Variables**

Pulse rate, systolic BP, diastolic BP, O<sub>2</sub> saturation were recorded at 0 min, 5 min, 15 min, 30 min, 60 min, 2 hours, 6 hours, 12 hours, 24 hours.

Time of Assessment	Mean ± SD		P value	Significance
	Bupivacaine	Bupivacaine - Fentanyl		
0 min	77 ± 6.8	75 ± 6.6	>0.05	NS
5 min	77 ± 6.6	76 ± 6.7	>0.05	NS
15 min	76 ± 6.5	76 ± 6.4	>0.05	NS
30 min	76 ± 6.8	76 ± 6.7	>0.05	NS
60 min	76 ± 6.6	75 ± 6.2	>0.05	NS
2 hrs	77 ± 6.5	75 ± 5.6	>0.05	NS
6 hrs	77 ± 6.4	76 ± 5.6	>0.05	NS
12 hrs	76 ± 6.2	74 ± 6.1	>0.05	NS
24 hrs	77 ± 6.5	76 ± 7.8	>0.05	NS

**Table 2. Pulse Rate (beats / min)**

In group B, the mean pulse rate ranged from 76 ± 6.2 to 77 ± 6.8 beats / min. In group BF, the mean pulse rate ranged from 74 ± 6.1 to 76 ± 6.7 beats / min. The statistical analysis by student’s unpaired ‘t’ test showed that there was no significant difference in pulse rate between the two groups (p > 0.05).

**Systolic Blood Pressure**

Time of Assessment	Mean ± SD		P Value	Significance
	Bupivacaine (in mm of Hg)	Bupivacaine-Fentanyl		
0 min	117 ± 9.9	118 ± 9.5	>0.05	NS
5 min	118 ± 10.1	117 ± 10.5	>0.05	NS
15 min	118 ± 10.1	118 ± 10.3	>0.05	NS
30 min	118 ± 10.3	118 ± 9.9	>0.05	NS
60 min	118 ± 9.9	117 ± 9.7	>0.05	NS
2 hrs	118 ± 9.6	117 ± 9.7	>0.05	NS
6 hrs	116 ± 9.3	118 ± 9.6	>0.05	NS
12 hrs	117 ± 9.8	116 ± 10.0	>0.05	NS
24 hrs	117 ± 9.4	116 ± 9.4	>0.05	NS

**Table 3. Systolic Blood Pressure (mm of Hg)**

Time of Assessment	Mean $\pm$ SD		p Value	Significance
	Bupivacaine	Bupivacaine-Fentanyl		
0 min	76 $\pm$ 7.71	75 $\pm$ 7.11	> 0.05	NS
5 min	76 $\pm$ 7.56	76 $\pm$ 7.59	> 0.05	NS
15 min	76 $\pm$ 7.21	76 $\pm$ 7.31	> 0.05	NS
30 min	75 $\pm$ 6.59	76 $\pm$ 7.18	> 0.05	NS
60 min	77 $\pm$ 7.29	76 $\pm$ 7.42	> 0.05	NS
2 hrs	77 $\pm$ 7.40	76 $\pm$ 7.58	> 0.05	NS
6 hrs	76 $\pm$ 7.33	76 $\pm$ 7.39	> 0.05	NS
12 hrs	76 $\pm$ 7.75	76 $\pm$ 7.83	> 0.05	NS
24 hrs	76 $\pm$ 6.87	76 $\pm$ 6.93	> 0.05	NS

**Table 4. Diastolic Blood Pressure (mm of Hg)**

In group B, the mean diastolic blood pressure ranged from 75  $\pm$  6.6 to 77  $\pm$  7.4 mm of Hg. In group BF, DBP ranged from 75  $\pm$  7.11 to 76  $\pm$  7.59 mm of Hg. The statistical analysis by unpaired student's 't' test showed that there was no significant difference in systolic blood pressure between two groups ( $p > 0.05$ )

Time of Assessment	Mean $\pm$ SD		p Value	Significance
	Bupivacaine	Bupivacaine-Fentanyl		
0 min	99.7 $\pm$ 0.57	99.7 $\pm$ 0.59	> 0.05	NS
5 min	99.8 $\pm$ 0.51	99.7 $\pm$ 0.54	> 0.05	NS
15 min	99.7 $\pm$ 0.63	99.7 $\pm$ 0.65	> 0.05	NS
30 min	99.7 $\pm$ 0.65	99.8 $\pm$ 0.53	> 0.05	NS
60 min	99.7 $\pm$ 0.58	99.8 $\pm$ 0.4	> 0.05	NS
2 hrs	99.7 $\pm$ 0.64	99.8 $\pm$ 0.48	> 0.05	NS
6 hrs	99.7 $\pm$ 0.56	99.8 $\pm$ 0.47	> 0.05	NS
12 hrs	99.7 $\pm$ 0.75	99.8 $\pm$ 0.55	> 0.05	NS
24 hrs	99.7 $\pm$ 0.53	99.8 $\pm$ 0.53	> 0.05	NS

**Table 5. Oxygen Saturation (%)**

In group B, the mean O<sub>2</sub> saturation ranged from 99.7  $\pm$  0.57% to 99.8  $\pm$  0.51%. In group BF, the mean O<sub>2</sub> saturation ranged from 98  $\pm$  0.5%. The statistical analysis by students unpaired 't' test showed that there was no significant difference in O<sub>2</sub> saturation between the two groups ( $p > 0.05$ ).

## DISCUSSION

Brachial plexus block is commonly given for upper limb surgeries for analgesia and anaesthesia as it carries less risk compared to general anaesthesia. Various adjuvant drugs like Opioids, Clonidine, Neostigmine and Hyaluronidase have been evaluated in conjunction with local anaesthetics to enhance the onset of analgesia and prolong the duration of analgesia. The primary effects of opioid antinociception are mediated at central or spinal cord level. Exact mechanism of action of opioids at peripheral nerve is still uncertain. Evidences have begun to support the presence of peripheral opioid receptors.<sup>10,11,12,13,14</sup> So the possible mechanism of prolonged analgesia by peripheral opioid administration could be through direct binding at opioid receptors of dorsal nerve root aided by axonal flow, diffusion through brachial plexus sheath to extradural or subarachnoid space to dorsal horn and central action after peripheral systemic uptake.<sup>15</sup>

Fentanyl, a phenylpiperidine derivative, is known to produce antinociception and enhance the effect of local anaesthetics when given epidurally or intrathecally. Fentanyl is a highly selective  $\mu$  receptor agonist, which is mainly responsible for its analgesic properties.

Hence an attempt has been made to assess the efficacy of Fentanyl as an adjuvant to Bupivacaine (0.25%) in brachial plexus block (axillary approach) in terms onset time, duration of analgesia and sedation. Haemodynamic variables and rescue analgesic requirements in first 24 hours were also studied.

A total of 100 patients within the age group of 15-55 were included in the study, 50 in each group. Out of which the mean age of group B (receiving only Bupivacaine) was 34.3  $\pm$  11.89 years and the mean age of group BF (receiving Fentanyl with Bupivacaine) was 32.3  $\pm$  10.51 years. Hence both groups were comparable in regard to age. Male to female ratio was almost same.

In our study we found that the addition of fentanyl to local anaesthetics in brachial plexus block caused significant prolongation of duration of analgesia but delayed the onset of both sensory and motor blockade compared to local anaesthetics alone. Onset of sensory block (group BF, 24.82  $\pm$  1.66 min; group B, 19.08  $\pm$  1.7 min). Onset of motor block (group BF, 16.48  $\pm$  2.62 min; group B, 15.30  $\pm$  2.09 min).

In our study addition of fentanyl to local anaesthetics caused a delay in onset of both sensory and motor blockade. The change in pH of the anaesthetic solution

resulting in slower penetration of nerve membrane by local anaesthetics could be responsible for this effect. Alkalinisation of local anaesthetic agents in nerve block has been shown to improve onset, quality and duration of analgesia.<sup>16,17,18,19</sup>

The same observation is concluded in a study by Tejwant Rajkhowa, Nilotpal Das, Samit Parua, et al,<sup>8</sup> on effect of fentanyl as an adjuvant for brachial plexus block, single blinded study 66 ASA I and II patients aged 18-65 years were included and were divided into 2 groups, group R (35) and RF (31). Supraclavicular brachial plexus block was performed in the group R using 0.5% ropivacaine 30 ml plus 1 ml NS (total 31 ml) and in group RF received 0.5% Compared to group R, group RF showed a significant greater duration of sensory and motor blockade ropivacaine plus 50 micrograms fentanyl in 1 ml NS (total 31 ml) in brachial plexus block. The authors concluded that the addition of fentanyl (adjuvant) to ropivacaine used for brachial plexus block may prolong the duration of sensory and motor block but may delay the onset of sensory and motor block compared to ropivacaine used alone.

Kohli Nishikawa et al<sup>20</sup> reported a reduction in pH by addition of fentanyl to lignocaine solution. In their study on fentanyl with lignocaine in axillary brachial plexus block, they concluded that decrease in pH of lignocaine from 6.2 to 5.2 by addition of 100µg of fentanyl may have resulted in slower onset of analgesia. There are reports of no improvement with alkalinisation also.<sup>21,22</sup> Further studies comparing the effects of addition of fentanyl to local anaesthetic using different pH solution are required to confirm this hypothesis.

In our study duration of motor blocks were different between the groups. (Group BF, 7.23 ± 1.01 hrs; group B, 6.17 ± 0.77 hrs).

In our study, the mean duration of sensory block (i.e. time elapsed from time of injection to appearance of pain requiring analgesia) was significantly higher ( $p < 0.05$ ) in group BF than in group B. (group BF, 13.65 ± 2.01 hrs; group B, 6.87 ± 0.89 hrs).

A study was conducted by Karakaya D, Büyükgöz F, Barış S, et al<sup>5</sup> to assess the efficacy of fentanyl as an adjuvant to bupivacaine in axillary plexus block. Sixty patients were randomly allocated to 3 groups and received axillary brachial plexus block with 40 mL bupivacaine 0.25% (group B), 40 mL bupivacaine 0.25% with fentanyl 2.5 microg/mL (group BF), or 40 mL bupivacaine 0.125% with fentanyl 2.5 microg/mL (group DBF). The onset times and the duration of sensory and motor blocks, duration of analgesia, hemodynamic parameters, and adverse events were noted. The mean duration of sensory block and analgesia were longer in group BF (hours and 20.9 hours) than group B (6.9 hours and 11.6 hours) and DBF (5.9 hours and 12.0 hours) ( $P < .01$ ,  $P < .001$ , respectively). The mean duration of motor block was also longer in group BF (10.7 hours) than group B (4.9 hours) ( $P < .01$ ). The duration of sensory and motor block are comparable to our study.

In our study, the number of patients who required rescue analgesia and the mean number of supplemental analgesic boluses required were also significantly lower in patients in Group BF. Similar observation was made in the above mentioned study by Karakaya D, Büyükgöz F, Barış S, et al<sup>5</sup> Fentanyl used with bupivacaine in our study prolonged the duration of sensory and motor blockade, probably by directly binding with opioid binding sites on the dorsal nerve roots aided with these axonal transport or by diffusing into surrounding tissues and subsequently into the epidural and subarachnoid spaces, it may also have been central opioid receptor mediated after systemic absorption of fentanyl.

Studies by Viel et al<sup>23</sup> on use of opioids for brachial plexus block have reported to prolong the analgesic duration with or without the use of local anaesthetics. Madusudhan et al.<sup>24</sup> demonstrated a significant increase in the duration of sensory, motor blockade on addition of fentanyl to ropivacaine 0.75% for brachial plexus blocks compared to ropivacaine used alone, which were similar to our study results. In our study, the addition of fentanyl to local anaesthetics for brachial plexus block (BF group) improved the success rate of nerve block.

Chavan et al<sup>6</sup> in their study on addition of 50g fentanyl to local anaesthetics in brachial plexus block showed an increase in mean duration of analgesia compared to control group.

Rajkhowa et al<sup>8</sup> demonstrated improved success rate and duration of analgesia with addition of 50µg of fentanyl to 0.5% ropivacaine in supraclavicular brachial plexus block. Prolongation of postoperative analgesia was reported in other studies also.<sup>25</sup> In our study we observed a significant prolongation of duration of analgesia with addition of fentanyl to local anaesthetics. Murphy DB et al<sup>4,9</sup> in their systematic review on analgesic adjuncts for brachial plexus block pointed out that evidences for analgesic benefit with addition of opioids in brachial plexus block over systemic opioids are minimal.

We studied Fentanyl at a dose of 2.5 µg/ml, as others have used the same dosage in central neuraxial block without any significant adverse effects. In our study, sedation scores were higher in patients in Group BF compared to Group B, 15 min after injecting the drug until 60 min after injection. Similar observation was made in the above-mentioned study by Karakaya D, Büyükgöz F, Barış S, et al.<sup>5</sup> This may have been due to partial vascular uptake of Fentanyl, and its transport to the central nervous system where it acts and produces sedation. The limited duration of sedation could be explained by the fact that Fentanyl is lipophilic and diffuses faster into the blood vessels, by its rapid clearance ( $6-11 \text{ mL.kg}^{-1}.\text{min}^{-1}$ ) and short half-life (1-2 hrs.). Though mean sedation score in group BF was higher as compared to group B ( $P < 0.05$ ), we did not observe clinically significant sedation in patients in group BF. No patient experienced airway compromise or required airway assistance. This mild sedation was actually desirable during that period.

**CONCLUSION**

We found that the addition of fentanyl 2.5 µg/ml added to 40 ml of 0.25% bupivacaine in axillary approach of brachial plexus block caused significant prolongation of duration of sensory and motor block ( $p < 0.05$ ) but delayed the onset of both sensory and motor blockade compared to bupivacaine alone and reduced requirements for rescue analgesics.

**REFERENCES**

- [1] Bone HG, Van Aken H, Brooke M, et al. Enhancement of axillary brachial plexus block anaesthesia by coadministration of neostigmine. *Reg Anesth Pain Med* 1999;24(5):405-410.
- [2] Bazin JE, Massoni C, Bruelle P, et al. The addition of opioids to local anaesthetics in brachial plexus block: the comparative effects of morphine, buprenorphine and sufentanil. *Anaesthesia* 1997;52(9):858-862.
- [3] Keeler JF, Simpson KH, Ellis FR, et al. Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block. *Br J Anaesth* 1992;68(1):68-71.
- [4] Culebras X, Van Gessel E, Hoffmeyer P, et al. Clonidine combined with a long acting local anesthetic does not prolong post-operative analgesia after brachial plexus block but does induce haemodynamic changes. *Anesth Analg* 2001;92(1):199-204.
- [5] Karakaya D, Büyükgöz F, Barış S, et al. Addition of fentanyl to bupivacaine prolongs anesthesia and analgesia in axillary brachial plexus block. *Reg Anesth Pain Med* 2001;26(5):434-438.
- [6] Chavan SG, Koshire AR, Panbude P. Effect of addition of fentanyl to local anesthetic in brachial plexus block on duration of analgesia. *Anesth Essays Res* 2011;5(1):39-42.
- [7] Karan D, Swaro S, Banerjee S. Comparison of fentanyl and dexmedetomidine as an adjuvant to bupivacaine in supraclavicular brachial plexus block: a randomized-double blind prospective study. *Asian J Pharm Clin Res* 2016;9(5):74-77.
- [8] Rajkhowa T, Das N, Parua S, et al. Fentanyl as an adjuvant for brachial plexus block: a randomized comparative study. *Int J Clin Trials* 2016;3(2):64-67.
- [9] Munipalle S, Gonapa B. Effect of Addition of fentanyl on the onset and duration of action of ropivacaine in brachial plexus block. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)* 2017;16(1):109-112.
- [10] DeJong RH, Wagman IH. Physiological mechanism of peripheral nerve block by local anesthetics. *Anesthesiology* 1963;24:684-727.
- [11] Stein C. Peripheral mechanisms of opioid analgesia. *Anesth Analg* 1993;76(1):182-191.
- [12] Gissen AJ, Gugino LD, Datta S, et al. Effects of fentanyl and sufentanil on peripheral mammalian nerves. *Anesth Analg* 1987;66(12):1272-1276.
- [13] Fields HL, Emson PC, Leigh BK, et al. Multiple opiate receptor sites on primary afferent fibres. *Nature* 1980;284(5754):351-353.
- [14] Stein C, Lang LJ. Peripheral mechanisms of opioid analgesia. *Curr Opin Pharmacol* 2009;9(1):3-8.
- [15] Wajima Z, Shitara T, Nakajima Y, et al. Comparison of continuous brachial plexus infusion of butorphanol, mepivacaine and mepivacaine-butorphanol mixtures for post-operative analgesia. *Br J Anaesth* 1995;75(5):548-551.
- [16] Nishikawa K, Kanaya N, Nakayama M, et al. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. *Anesth Analg* 2000;91(2):384-387.
- [17] Tetzlaff JE, Yoon HJ, Brems J, et al. Alkalinization of mepivacaine improves the quality of motor block associated with interscalene brachial plexus anesthesia for shoulder surgery. *Reg Anesth* 1995;20(2):128-132.
- [18] Gormley WP, Hill DA, Murray JM, et al. The effect of alkalinisation of lignocaine on axillary brachial plexus anaesthesia. *Anaesthesia* 1996;51(2):185-188.
- [19] Kanaya N, Imaizumi H, Matsumoto M, et al. Evaluation of alkalinized lidocaine solution in brachial plexus blockade. *J Anesth* 1991;5(2):128-131.
- [20] Nishikawa K, Kanaya N, Nakayama M, et al. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. *Anesth Analg* 2000;91(2):384-387.
- [21] Chow MY, Sia AT, Koay CK, et al. Alkalinization of lidocaine does not hasten the onset of axillary brachial plexus block. *Anesth Analg* 1998;86(3):566-568.
- [22] Candido KD, Winnie AP, Covino BG, et al. Addition of bicarbonate to plain bupivacaine does not significantly alter the onset or duration of plexus anesthesia. *Reg Anesth* 1995;20(2):133-138.
- [23] Viel EJ, Eledjam JJ, De La Coussaye JE, et al. Brachial plexus block with opioids for postoperative pain relief: comparison between buprenorphine and morphine. *Reg Anesth* 1989;14(6):274-278.
- [24] Madhusudhana R, Kumar K, Kumar R, et al. Supraclavicular brachial plexus block with 0.75 % ropivacaine and with additives tramadol, fentanyl- a comparative pilot study. *Int J Biol Med Res* 2011;2(4):1061-1063.
- [25] Sindjelic RP, Vlajkovic GP, Davidovic LB, et al. The addition of fentanyl to local anesthetics affects the quality and duration of cervical plexus block: a randomized, controlled trial. *Anesth Analg* 2010;111(1):234-237.