

## CLONIDINE AND FENTANYL AS ADJUVANTS WITH 0.5% BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK FOR UPPER LIMB SURGERY

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### Abstract

**Background:** Adjuncts added to local anaesthetics improve the quality of regional blocks. We compared clonidine and fentanyl as adjuncts to bupivacaine with respect to onset, completion, duration of sensory and motor blockade, duration of analgesia, haemodynamics and complications. **Materials and Methods:** Eighty American Society of Anaesthesiologists Grade I and II patients scheduled for upper limb surgery under supraclavicular brachial plexus block were allocated to two equal groups by randomisation and double blinding. Both received 25ml of 0.5% bupivacaine with 1µg/kg of clonidine in BC group and 1µg/kg of fentanyl in BF group. Onset, completion, duration of sensory and motor blockade, duration of analgesia, haemodynamics and complications were studied. Statistical analysis was done using Chi-square test and Standard t-test. **Result:** Onset and completion of sensory and motor block was significantly lower in BC group ( $4.75 \pm 0.51$  and  $19.98 \pm 0.97$ ) and ( $6.40 \pm 0.63$  and  $23.50 \pm 1.26$ ) compared to BF group ( $7.10 \pm 0.84$  and  $22.95 \pm 1.08$ ) and ( $8.85 \pm 0.95$  and  $26.50 \pm 1.22$ ) ( $P = 0.001$ ). Duration of sensory and motor block was significantly higher in BC group ( $489.75 \pm 21.45$ ) and ( $476.00 \pm 20.54$ ) compared to BF group ( $398.20 \pm 19.84$ ) and ( $395.00 \pm 19.55$ ) ( $P = 0.001$ ). Duration of analgesia was significantly higher in BC group ( $507.63 \pm 21.36$ ) compared to BF group ( $425.75 \pm 20.05$ ) ( $P = 0.001$ ). No significant adverse effects were noted. **Conclusion:** Clonidine as an adjuvant has an extra edge over fentanyl in terms of faster onset of sensory, motor block and longer duration of analgesia.

## INTRODUCTION

Brachial plexus block is a popular and widely employed regional nerve block technique for peri-operative anaesthesia for surgery of the upper extremity. It prevents the untoward effects of anaesthetic drugs used during general anaesthesia as well as the stress of laryngoscopy and tracheal intubation. This technique is particularly beneficial in patients with various cardio-respiratory comorbidities.

Bupivacaine is frequently used as a local anaesthetic agent because of its favourable ratio of sensory to motor neural blockade and longer duration of action.<sup>[1]</sup> The goal of adding novel adjuncts to local anaesthetics is to prolong the analgesic effect and also allow a reduction in the total dose of the local anaesthetic. Many drugs like neostigmine, opioids, steroids, hyaluronidase, midazolam, clonidine,

dexmedetomidine etc. have been added to improve the quality and duration of action as well as aid in postoperative analgesia along with minimizing the limiting factors such as delayed onset, patchy or incomplete analgesia.<sup>[2]</sup>

Fentanyl, a short acting opioid is widely used as an adjunct to bupivacaine to prolong the duration of sensory and motor blockade and also provide postoperative analgesia.<sup>[3]</sup>

Clonidine, an alpha 2 adrenergic agonist has become popular due to its ability to prolong the duration of nerve block due to its contributory centrally mediated action as well.<sup>[4]</sup>

Despite the wide popularity of supraclavicular block for upper limb surgery, there is little evidence comparing the effectiveness of fentanyl and clonidine with bupivacaine, either in clinical practice or in studies.

The aim of the present study was to evaluate the clinical effectiveness and blockade quality of bupivacaine when used with adjuvants such as fentanyl and clonidine for upper limb surgery. Hence we conducted a study on two groups using 25ml of 0.5% bupivacaine with either 1µg/kg of clonidine or 1µg/kg of fentanyl to compare the effects of these two adjuvants added to bupivacaine in supraclavicular brachial plexus block for upper limb surgery under ultrasound guidance.

## MATERIALS AND METHODS

A randomised, double blinded prospective study was conducted on eighty American society of Anaesthesiologists Grade I and II patients of either sex, aged 16-60 years who were scheduled for upper limb surgery under supraclavicular brachial plexus block at a tertiary care teaching hospital after obtaining approval of the Institutional ethical committee as well as written informed consent from the patients.

Patients who refused to enrol in the study, or the ones unable to understand the protocol, coagulopathy, a known drug sensitivity to the drugs used in the study, pregnant and breastfeeding patients, infection at the site of injection, patients with a previous or new onset sensory or motor loss in the limb to be operated upon, chronic opioid or NSAID user (> 3 months duration) were excluded from the study.

Participants were allocated to two equal groups of 40 each using a computer generated random number list. Group A patients received 25 ml of 0.5% bupivacaine with 1µg/kg IBW of clonidine (addressed as BC in the study) and Group B patients received 25 ml of 0.5% bupivacaine and 1µg/kg IBW of fentanyl (addressed as BF in the study). The allocation sequence was generated by the author entrusted with the statistical analysis. The anaesthesiologist administering the block and observing the effects received serially numbered sealed envelopes indicating A or B codes for the anaesthetic mixture to be administered. The A and B syringes were loaded with drugs by another anaesthesiologist not involved in administering the injections and in further evaluation of the patients. All observations of the study were also recorded in a blinded manner.

A detailed pre-anaesthetic evaluation was carried out to optimize the patients for any significant comorbidity. Patients were given tablet alprazolam 0.5mg and tablet ranitidine 150mg as premedication the night prior to the surgery and were advised a minimum of 8 hours of fasting. On arrival to the pre prepared operating room, the patient and the limb to be operated upon was verified, all standard ASA monitors were connected, an intravenous access was secured in the unaffected limb and an appropriate IV fluid was started. All drugs for the management of local anaesthetic systemic toxicity, the anaesthesia machine, emergency source of oxygen, laryngoscopes, appropriate sized endotracheal tubes

and connectors were kept ready for emergency resuscitation. The procedure was clearly explained and then the patient was appropriately positioned with the head turned to the contralateral side and the arm to be anaesthetized was adducted. The part was painted and draped under all aseptic precautions. In both the groups, supraclavicular brachial plexus block was performed using 22 gauge, 10 centimeter sonoplex needle under ultrasound guidance (using Sonosite Micromaxx portable ultrasound machine with a linear probe of 7.5MHz) by the same anaesthesiologist, who used the same technique of administering the block in all the patients.

The test drug was injected slowly following intermittent negative aspiration for blood, as per the randomly allocated group. Completion of injection was taken as time 0 - (T<sub>0</sub>). Following injection of the drug combination, the area was massaged to help the solution track along the plexus. During the conduct of the block and thereafter, the patient was observed vigilantly for any complications of the block (like arterial puncture) and for the toxicity of the drugs injected (like bradycardia, hypotension, nausea, vomiting, itching, etc.).

The patients were monitored for heart rate (HR), non-invasive systolic and diastolic blood pressure (SBP and DBP), mean arterial blood pressure (MAP) at an interval of 5 minutes for first half an hour and thereafter every 15 minutes intraoperatively. Electrocardiogram (ECG) and pulse oxygen saturation (SPO<sub>2</sub>) was monitored on a continuous basis intraoperatively. Sensory and motor block evaluation was done every minute after administering the block until complete sensory and motor block or 15 minutes, whichever was earlier.

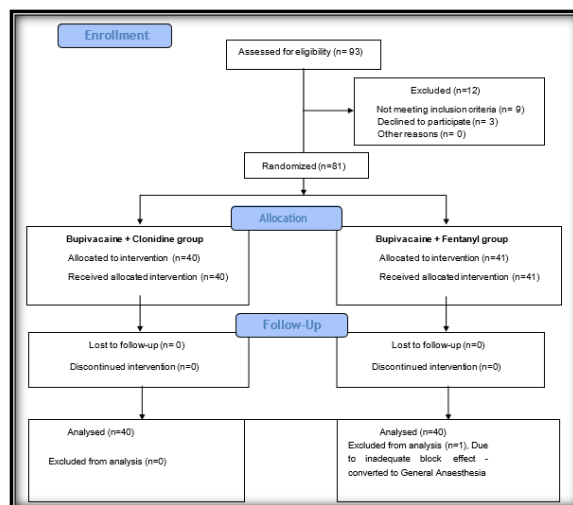
The sensory block was evaluated using the pin-prick method (Hollmen's Scale): Grade 1 - Normal sensation of pin prick. 2 - Pin prick felt as sharp pointed but weaker compared with the same area in the other extremity. 3 - Pin prick felt as touch with blunt object. 4 - No perception of pin prick. Onset of sensory blockade was defined as the time taken from the completion of injection of the drug (T<sub>0</sub>) to the time when sensory block began to be detected, i.e a minimum of grade 2 and the time to complete sensory block was taken from T<sub>0</sub> to the achievement of a grade 3 in the distribution of all the major nerves. Total duration of analgesia was taken from the time of complete sensory block to the request of first rescue analgesic or a numeric pain rating scale  $\geq 4$ .

The motor block was evaluated using the Modified Bromage Scale Score 1- Partial block : total forearm and partial arm flexion. 2 - Almost complete block : inability to flex the arm and decreased ability to flex the forearm. 3 - Total block : inability to flex both the arm and forearm. Post-surgery, in the recovery room, patients were asked to rate their pain on a 0-10 numeric pain rating scale. (0 - no pain and 10 - worst pain imaginable). Pain was assessed regularly every 30 min for the first 3 hours and then every third hourly for the next 12 hours. The duration of motor block was assessed at T<sub>0</sub>, every minute for 15

minutes after administering the block or until complete motor block was attained, whichever was earlier, thereafter every 30minutes for first 3hours and then third hourly for the next 12 hours by asking the patient to flex his arm and forearm. The time when the patient could flex his arm and forearm completely was recorded and taken as cessation of the motor block effect. Duration of motor block was defined as the time interval between the drug administration and the recovery of complete motor power of the upper limb. Injection diclofenac sodium aqueous 75mg intravenously was given when the numeric pain rating score was  $\geq 4$ . The time between the end of local anaesthetic administration and first rescue analgesic administration was recorded as the duration of analgesia.

Data was recorded in a master chart in MS Excel program. Data collected was analysed using Statistical Product for Social Sciences (SPSS) Version 20.0. Continuous variables were presented as mean  $\pm$  SD, qualitative variables were described as number (percentage). Normally distributed data was compared using independent t-test. Chi-square test and student t-test was applied as appropriate. The p-

value was determined to evaluate the level of significance. The statistical test was considered significant at P value  $< 0.05$  and P value  $< 0.001$  was considered highly significant.



**Figure 1: Consort Flow Diagram**

## RESULTS

**Table 1: Comparison of demographic parameters between the two groups**

Parameter	BC		BF		P value
	Mean	SD	Mean	SD	
Age (years)	45.13	15.49	44.98	16.31	0.97
Weight (kg)	63.08	9.25	64.40	8.10	0.49
Height (cm)	166.28	7.42	167.60	7.26	0.42
Gender					
Male	17		18		
Female	23		22		0.78
Total	40		40		
ASA PS					
I	24		25		
II	16		15		0.80
Total	40		40		

Statistically no significant difference was seen between the two groups with respect to age, weight, height, gender and ASA physical status.

**Table 2: Comparison of sensory and motor block parameters between the two groups**

Sensory Block	BC		BF		P value
	Mean	SD	Mean	SD	
Time of Onset (minutes)	4.75	0.51	7.10	0.84	0.001
Time of Completion (minutes)	19.98	0.97	22.95	1.08	0.001
Total Duration (minutes)	489.75	21.45	398.20	19.84	0.001
Motor Block					
Time of Onset (minutes)	6.40	0.63	8.85	0.95	0.001
Time of Completion (minutes)	23.50	1.26	26.50	1.22	0.001
Total Duration (minutes)	476.00	20.54	395.00	19.55	0.001

The onset and completion of sensory and motor block was faster in the BC group when compared to the BF group. The duration of sensory and motor block was longer in the BC group when compared to the BF group.

**Table 3: Comparison of duration of analgesia between the two groups**

	BC		BF		P value
	Mean	SD	Mean	SD	
Duration of analgesia	507.63	21.36	425.75	20.05	0.001

BC group had a longer duration of the period of analgesia in comparison with BF group.

Kaplan – Meier curve depicting the time at which the numeric pain rating score was  $\geq 4$  in each group.

Patients in the BC group attained a numeric pain rating score of  $\geq 4$  later in the postoperative period when compared to patients in the BF group. The patients in the BC group required lesser number of rescue analgesias within the first 12 hours of surgery when compared to the BF group.

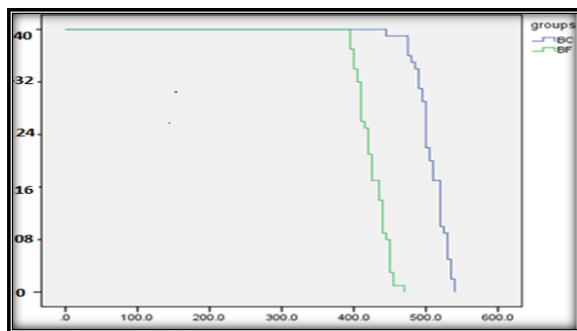


Figure 2:

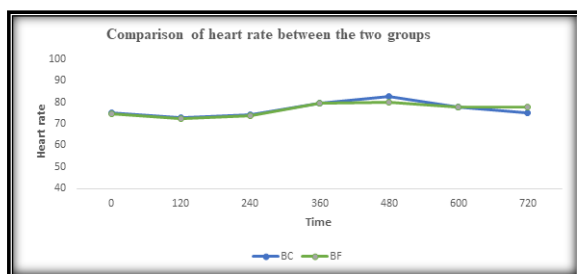


Figure 3:

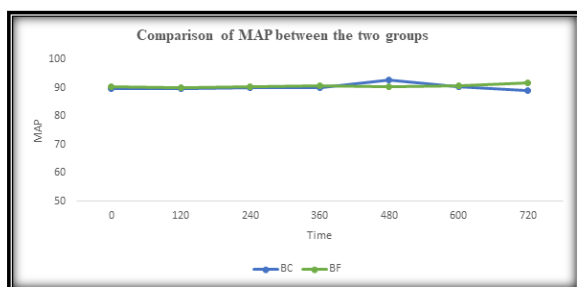


Figure 4:

No hemodynamic instability was seen in both the groups.

#### Adverse effects

No significant difference in the adverse effects was noted amongst the 2 groups. Nausea was seen in 1 patient each among the 2 groups and hoarseness of voice in 1 patient in the bupivacaine fentanyl group.

## DISCUSSION

Pain is an inevitable component of the postoperative period. Although pain has teleological function in warning patients about potential injury, it also exerts deleterious effects on respiratory, cardiovascular, neuroendocrine, gastrointestinal and other systems of the body.<sup>[5]</sup> Hence an effective pain relief after surgery is essential for optimal care of the patient. Role of peripheral nerve block has expanded from the operating suite into arena of postoperative and

chronic pain management. Typical features of peripheral nerve block include rapid onset, dense anaesthesia and postoperative analgesia. Several studies concluded that various adjuncts used in supraclavicular brachial plexus block prolong the duration of local anaesthetics in the block. Amongst the additives fentanyl and clonidine have been separately used in various studies to prolong the duration of analgesia.<sup>[6-12]</sup> Tejwant Rajkhowa et al.<sup>[7]</sup> in their study concluded that fentanyl added to ropivacaine showed a significantly greater duration of sensory and motor blockade when compared to ropivacaine alone. The mechanism of action of fentanyl in supraclavicular brachial plexus block is due to direct binding on the dorsal nerve roots along with axonal transport or by diffusion into the surrounding tissues and eventually into the epidural and subarachnoid spaces. Fentanyl may also have a local-anaesthetic like action and central opioid receptor effects may be mediated by systemic absorption.<sup>[13]</sup>

Similarly, clonidine was studied by Nama Nagarjuna Chakravarthy et al.<sup>[12]</sup> and they concluded that clonidine added to bupivacaine prolongs the duration of the block when compared to bupivacaine alone. The mechanism by which alpha 2 adrenoreceptor agonists produce analgesia and sedation is multifactorial and has not been fully understood. They have peripheral and central actions. Peripherally they reduce the release of norepinephrine and cause inhibitory effect on the nerve action potentials, thereby producing analgesia. Centrally they act at locus coeruleus and activate the alpha 2 adrenoreceptors and produce analgesia and sedation by inhibiting the release of substance P at the level of the dorsal root neuron. An increase in the potassium ion channel conductance was seen with stimulation of alpha 2 adrenoreceptors.<sup>[14]</sup> There were very few studies comparing fentanyl and clonidine with 0.5% bupivacaine in supraclavicular brachial plexus block.<sup>[15-17]</sup> Hence we conducted a study to compare the two drugs added as adjuvants in supraclavicular brachial plexus block. The volume of 0.5% bupivacaine taken in this study was 25ml which was similar to the study conducted by Dipti Mundadha et al.<sup>[16]</sup> who concluded adequacy of the volume for intraoperative and postoperative analgesia with the use of ultrasonographic guidance in contrast to the study conducted by Nasir Uddin et al.<sup>[15]</sup> wherein 38ml of local anaesthetic solution gave similar results.

From the paraesthesia seeking techniques described by Winnie,<sup>[18]</sup> in the mid twentieth century and the studies conducted by Moore et al.<sup>[19]</sup> and Matthes et al.<sup>[20]</sup> which encountered complications such as pneumothorax due to the landmark guided paraesthesia technique to the popularization of the nerve stimulator and the introduction of ultrasound guidance, anaesthesiologists have been benefited from technology's evolution. In the recent years, a number of prospective randomised studies on brachial plexus block under ultrasound guidance

have been conducted. Ultrasound increases the rate of success of the block together with reducing complications such as pneumothorax and arterial puncture.<sup>[21]</sup>

Hence we used an ultrasonographically guided supraclavicular brachial plexus block in our study to minimize the complications associated with the block.

In our study, the baseline demographic data such as age, gender, weight, height and ASA PS grading were comparable between the two groups. [Table 1].

The mean time of onset of sensory block in our study was 4.75 minutes  $\pm$  0.51 in the bupivacaine clonidine group and 7.10 minutes  $\pm$  0.84 in the bupivacaine fentanyl group (P = 0.001) which was statistically significant.

The mean time of completion of sensory block was 19.98 minutes  $\pm$  0.97 and 22.95 minutes  $\pm$  1.08 (P = 0.001) respectively in the bupivacaine clonidine and bupivacaine fentanyl group which was statistically significant.

The total duration of sensory block was 489.75 minutes  $\pm$  21.45 and 398.2 minutes  $\pm$  19.84 (P = 0.001) respectively in the bupivacaine clonidine and bupivacaine fentanyl group which was again statistically significant.

The mean time of onset and of motor block in our study was 6.40 minutes  $\pm$  0.63 in the bupivacaine clonidine group and 8.85 minutes  $\pm$  0.95 in the bupivacaine fentanyl group (p = 0.001) which was statistically significant.

The mean time of completion of motor block was 23.50 minutes  $\pm$  1.26 and 26.50 minutes  $\pm$  1.22 (P = 0.001) respectively in the bupivacaine clonidine and bupivacaine fentanyl group which was statistically significant.

The total duration of motor block was 476.00 minutes  $\pm$  20.54 and 395 minutes  $\pm$  19.55 (P = 0.001) respectively in the bupivacaine clonidine and bupivacaine fentanyl group which was again statistically significant. [Table 2]

These results were comparable to the study conducted by Nasir Uddin Ahmed et al,<sup>[15]</sup> comprising of 60 patients with Group A comprising 30 patients who received 2ml (100 $\mu$ g) of fentanyl and 38ml of 0.25% bupivacaine and 30 patients in Group B who received 2ml (150  $\mu$ g) clonidine and 38ml of 0.25% bupivacaine. The onset and duration of sensory block (8.9 mins  $\pm$  2.9 ,11.9 mins  $\pm$  2.7 and 364.5 mins  $\pm$  33.3, 558 mins  $\pm$  66.4) were significantly higher in Group B (clonidine group) than in Group A (fentanyl group) (P < 0.001)

The mean total duration of analgesia in our study was higher in the bupivacaine clonidine group (507.63 minutes  $\pm$  21.36) when compared to the bupivacaine fentanyl group (425.75 minutes  $\pm$  20.05), the P value being 0.001 which was statistically significant. [Table 3] These results were comparable to a study conducted by Dipti Mundhada, et al,<sup>[16]</sup> comprising of 70 patients, aged 18-60 years, randomly divided into 2 groups of 35 patients each. Group C received 25ml of 0.5% Bupivacaine + 1 $\mu$ g/kg body weight of

clonidine, whereas Group F received 25ml of 0.5% Bupivacaine + 1 $\mu$ g/kg body weight of fentanyl. The mean duration of analgesia was 13 hours 13 mins  $\pm$  52 mins and 11 hours 37 mins  $\pm$  1 hour 7 mins for clonidine and fentanyl group respectively.

Some studies reported the incidence of bradycardia and hypotension with alpha 2 adrenoreceptor agonists which was not seen in our study.<sup>[22]</sup>

Hemodynamic parameters were comparable between the two groups in our study (P > 0.05) [Figure 2, Figure 3] which was identical to the study conducted by Dipti Mundhada et al,<sup>[16]</sup> comprising of 70 patients, aged 18-60 years, randomly divided into 2 groups of 35 patients each. Group C received 25ml of 0.5% Bupivacaine + 1 $\mu$ g/kg body weight of clonidine, whereas Group F received 25ml of 0.5% Bupivacaine + 1 $\mu$ g/kg body weight of fentanyl. The study also concluded that hemodynamic parameters were comparable between the two groups.

2 patients (1 from bupivacaine clonidine and 1 from bupivacaine fentanyl group) experienced nausea which was treated with Inj. Ondansetron 4 mg IV. 1 patient in the bupivacaine fentanyl group experienced hoarseness of voice which was treated with Inj. Dexamethasone 8mg IV. There were no significant adverse events in any of the two groups which was comparable to the previous study conducted by Dipti Mundhada et al.<sup>[16]</sup> 1 patient had to be added to the bupivacaine fentanyl group due to inadequate block effect in whom the mode of anaesthesia was converted to general anaesthesia. No other major complications such as pneumothorax or arterial puncture were noted in our study due to the use of ultrasound guidance for the administration of the block.

## CONCLUSION

Our study concluded that both clonidine and fentanyl used as adjuvants to 0.5% bupivacaine in supraclavicular brachial plexus block for upper limb surgery prolong the duration of sensory, motor block and the duration of analgesia without causing significant adverse effects but clonidine as an adjuvant has an advantage over fentanyl in terms of faster onset of sensory and motor block and longer duration of postoperative analgesia.

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