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# Comparison of buprenorphine and clonidine when added to bupivacaine during supraclavicular brachial plexus block

**Nisha Saral Joseph[1], Kavitha Muthaiyan[1,*], Sureshbabu Krishnan[1], Balakrishnan Venkatesan[1] and Shankar R[2]**

[1]Department of Anaesthesia, Government Mohan Kumara Mangalam Medical College Hospital Salem, Tamil Nadu 636002, India
[2]Department of Preventive Medicine, Vinayaka Missions Kirupananda Variyar Medical College and Hospital, Salem, Tamil Nadu 636308, India

## Abstract

**Background:** During spinal and epidural anesthesia adding buprenorphine or clonidine as an adjuvant along with local anesthetic agent has given promising results in producing analgesia, whereas the same agent when used for brachial plexus block had shown mixed results. The study aimed to compare the anesthetic and analgesic properties of buprenorphine and clonidine when used as adjuvants along with bupivacaine during supraclavicular brachial plexus blockade.

**Methodology:** A double blinded randomized controlled trial was conducted for a period of one year. A total of 90 subjects were divided into three groups. All three groups patients received 0.3% bupivacaine as the anesthertic agent, the adjuvant used for group A patients was 1 ml normal saline, group B it was 1 ml of 300 mcg buprenorphine and group C patients received 1 ml of 150 mcg clonidine as adjuvant. Hemodynamic parameters, sensory and motor blockade levels along with the occurrence of adverse events were monitored at regular intervals among all the study subjects.

**Results:** Hemodynamic parameters were well maintained in all three groups without showing significant differences in the parameters. Patients in the buprenorphine group had an early onset of sensory block along with prolonged duration of block, whereas no significant changes reported with relation to motor block. As such there was no incidence of adverse events in any of the three groups.

**Conclusion:** Compared to clonidine, buprenorphine was found to be a better adjuvant to bupivacaine for producing analgesic effect.

***Keywords:*** brachial plexus block; buprenorphine; clonidine; sensory; motor block

## Introduction

Acute postoperative pain is a common symptom experienced by patients after any surgery which results as a part of body's physiological response to the tissues that were disturbed during the surgical procedure. The dorsal horn of the spinal cord is the place where the primary afferent nerves terminate, which indulge the pain modulating fibres along with the release of various neurotransmitters like glutamate, acetylcholine, serotonin, and norepinephrine that are responsible for pain [1].

As a part of treating the post-operative pain local anaesthetics are being used which acts by blocking the signal traffic to the dorsal horn thereby producing post-operative pain relief for the patients who had undergone surgery. Various research studies done in the past by adding analgesic agents along with regional anesthesia showed beneficial effects in the form of reducing the postoperative pain but there were adverse events reported related to either hemodynamic parameters or

***Corresponding author:** Dr. Kavitha Muthaiyan, Assistant Professor, Department of Anaesthesia, Government Mohan Kumara Mangalam Medical College Hospital Salem, Tamil Nadu 636002, India. Email: kavithaswaminathan.muthaiyan@gmail.com

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in prolonging the motor or sensory block. So the concept of lowering the concentration of anesthetic drugs had been tried by the recent researchers to ameliorate the incidence of these side effects [2].

Initially bicarbonate and epinephrine had been tried as adjuncts to local anesthestic drugs for regional blocks and it was found that bicarbonate had produced an early onset of action and epinephrine had prolonged the duration of action. In a similar way fentanyl and tramadol are now commonly being used as adjuvants for local anesthetic agents and had proved to be highly effective in producing analgesic effect during regional block [3, 4].

All the research so far conducted that by combining an analgesic with an anesthetic agent had significantly demonstrated an analgesic effect at spinal level, this had created a spark among the researchers to investigate further to find out whether these medications would also provide analgesic effects at the periphery [5]. The possible mechanisms that had been quoted for the analgesic drugs act when used in the peripheral block were either by systemic absorption or by facilitating the local anaesthetic drug or else by direct local action on the nerve itself. Different mechanisms were quoted by different studies and there was a huge difference in the study design which had created the interpretation more challenging [6-8].

Clonidine, a selective alpha 2 adrenergic agonist, when combined with local anaesthetic agent demonstrated a promising result in providing peripheral nerve blocks by lowering the onset time and producing a prolonged analgesic action in the post-operative period without causing side effects [9]. The usual dose of clonidine that is being regularly used is in the range between 0.1 and 0.5 $\mu$g/kg [10, 11].

Buprenorphine, a synthetic opiod, commonly used adjuvant in spinal anaesthesia acts via μ opioid receptors that are found in the dorsal horn of substantia gelatinosa. Buprenorphine had shown promising results in increasing the length and quality of analgesia in the entire post-operative period when injected intra-thecally, but some dose-related adverse effects have been reported such as pruritus, nausea, vomiting and rarely respiratory depression [12-14].

As of today, only few studies had been conducted using clonidine and buprenorphine as an adjuvant with bupivacaine during spinal anesthesia block [15-17]. Not much research has been done on brachial plexus block using these two agents, so the present study aimed to compare the analgesic effects of buprenorphine and clonidine when used with bupivacaine during brachial plexus blockade.

## Methodology

A double blinded randomized controlled trial, in which both the patient and the investigator are blinded, was conducted for a period of one year by the department of anesthesiology at a Government Mohan Kumaramangalam Medical College and Hospital, Tamil Nadu, between Jan 2023 and June 2023. The study was started after getting approval from the institutional ethics committee. The inclusion criteria for our study were fixed as patients aged more than 20 and less than 50 years with ASA grade either I or II. We made three groups with 30 patients in each group. Group A patients were considered as a control group for whom normal saline was used as an adjuvant, for group B we used 1 ml of 300 mcg buprenorphine and group C patients received 1 ml of 150 mcg clonidine as adjuvant. The exclusion criteria for the present study were patients aged less than 20 and more than 50, patients with any other co-morbid conditions, pregnant and lactating mothers.

After conducting a pre-operative anesthetic assessment for all patients, randomization was made using random number table for allocating the patients in the respective groups. Premedication was done with inj. atropine in the dosage of 0.02mg/kg.

Supraclavicular brachial plexus block was performed using a 22G hypodermic needle. Sensory and motor block was assessed using Hollmen scale. The first onset of pain in the postoperative period was recorded. Incidence of adverse events during intraoperative and post-operative period were recorded and treated accordingly.

All the data were entered and analyzed using SPSS version 24. Mean and SD were derived for all parametric variables and percentage for the frequency variables. Statistical inference was assessed using ANOVA and the difference between the groups was interpreted using Post hoc test of Bonferroni, by considering p value of <.05 as statistically significant.

## Results

Our study results showed that all the pre-anesthetic parameters such as hemodynamic variables along with their age, weight and duration of surgery among the three groups were almost similar and no statistical significance difference was observed between the groups (Table 1).

**Table 1:** Comparison of pre-anesthetic parameters among the study subjects between the three groups.

| *Variables* | *Group* | *Mean* | *S D* | *ANOVA 'F'* | *P value* |
|---|---|---|---|---|---|
| *Age* | | | | | |
| | A | 33.5 | 6.4 | 2.341 | 0.675 |
| | B | 39.1 | 7.6 | | |
| | C | 35.3 | 7.3 | | |
| *Weight* | | | | | |
| | A | 64.4 | 3.3 | 3.874 | 0.798 |
| | B | 63.2 | 3.6 | | |
| | C | 62.6 | 4.8 | | |
| *Pulse rate (Baseline)* | | | | | |
| | A | 82.5 | 3.6 | 1.286 | 0.719 |
| | B | 80.9 | 4.5 | | |
| | C | 81.7 | 3.3 | | |
| *MAP (Baseline)* | | | | | |
| | A | 92.8 | 1.7 | 0.295 | 0.724 |
| | B | 92.3 | 2.1 | | |
| | C | 91.8 | 1.8 | | |
| *SPO2* | | | | | |
| | A | 97.2 | 0.7 | 1.695 | 0.845 |
| | B | 98.3 | 0.8 | | |
| | C | 98.2 | 0.6 | | |
| *Duration of surgery (mins)* | | | | | |
| | A | 112.9 | 15 | 2.15 | 0.225 |
| | B | 107.8 | 14.7 | | |
| | C | 115.6 | 12.9 | | |

The hemodynamic parameters that were measured in our study were pulse rate, blood pressure, mean arterial pressure and Spo2. All these parameters were measured both during intra and post-operatively at regular intervals starting from 5 mins of administering the anesthetic agents and it was monitored once every 10 mins for the first one hour and then onwards hourly for the next 12 hours and 4$^{th}$ hourly till 24 hours. In our study it was found that throughout the entire intra and post-operative period the hemodynamic parameters were well maintained in all the three groups and there was no statistically significant difference observed at any point of time between the three groups related to their pulse rate, mean arterial pressure and SPO2 (table 2a, 2b and 2c).

**Table 2a:** Comparison of hemodynamic parameters between three groups at various time intervals (Pulse rate).

| *Pulse rate* | *Group* | *Mean* | *S D* | *F value* | *P value* |
|---|---|---|---|---|---|
| 5 Minutes | | | | | |
| | A | 83.9 | 4.3 | | |
| | B | 81.7 | 3.4 | 1.296 | 0.318 |
| | C | 84.8 | 2.9 | | |
| 10 Minutes | | | | | |
| | A | 83.9 | 6.3 | | |
| | B | 82.8 | 4.1 | 0.394 | 0.713 |
| | C | 83.9 | 3.6 | | |
| 20 Minutes | | | | | |
| | A | 84.1 | 4.4 | | |
| | B | 83.7 | 4.2 | 0.864 | 0.294 |
| | C | 85.1 | 3.3 | | |
| 30 Minutes | | | | | |
| | A | 85.3 | 3.2 | | |
| | B | 83.6 | 4.4 | 1.176 | 0.268 |
| | C | 85.1 | 3.6 | | |
| 1 Hour | | | | | |
| | A | 84.1 | 4.2 | | |
| | B | 83.7 | 3.3 | 1.386 | 0.326 |
| | C | 84.9 | 2.9 | | |
| 2 Hour | | | | | |
| | A | 84.1 | 4.1 | | |
| | B | 83.6 | 3.6 | 2.692 | 0.074 |
| | C | 85.9 | 2.8 | | |
| 3 Hour | | | | | |
| | A | 84.3 | 2.9 | | |
| | B | 83.8 | 4.1 | 1.291 | 0.242 |
| | C | 85.1 | 3.1 | | |
| 4 Hour | | | | | |
| | A | 85.1 | 2.2 | | |
| | B | 83.8 | 4.0 | 1.612 | 0.228 |
| | C | 85.4 | 3.1 | | |
| 5 Hour | | | | | |
| | A | 85.1 | 3.7 | | |
| | B | 82.9 | 5.0 | 1.812 | 0.158 |
| | C | 84.8 | 3.5 | | |

| | | | | | |
|---|---|---|---|---|---|
| 6 Hour | | | | | |
| | A | 85.2 | 3.1 | | |
| | B | 83.9 | 4.2 | 0.931 | 0.423 |
| | C | 84.9 | 3.1 | | |
| 8 Hour | | | | | |
| | A | 85.9 | 4.2 | | |
| | B | 83.9 | 4.0 | 0.929 | 0.314 |
| | C | 84.4 | 3.3 | | |
| 12 Hour | | | | | |
| | A | 84.8 | 4.3 | | |
| | B | 83.6 | 4.0 | 1.213 | 0.254 |
| | C | 84.6 | 3.2 | | |
| 16 Hour | | | | | |
| | A | 85.1 | 4.3 | | |
| | B | 83.6 | 3.8 | 0.729 | 0.459 |
| | C | 84.7 | 3.4 | | |
| 24 Hour | | | | | |
| | A | 85.9 | 4.1 | | |
| | B | 83.9 | 3.2 | 0.621 | 0.519 |
| | C | 85.2 | 3.8 | | |

**Table 2b:** Comparison of hemodynamic parameters between three groups at various time intervals (Mean arterial pressure).

| *MAP* | *Group* | *Mean* | *S D* | *F* | *P value* |
|---|---|---|---|---|---|
| 5 Minutes | | | | | |
| | A | 92.1 | 1.4 | 1.238 | 0.219 |
| | B | 91.2 | 2.2 | | |
| | C | 91.9 | 2.6 | | |
| 10 Minutes | | | | | |
| | A | 92.9 | 3.8 | 0.918 | 0.899 |
| | B | 93.1 | 1.2 | | |
| | C | 92.2 | 1.3 | | |
| 20 Minutes | | | | | |
| | A | 91.9 | 4.1 | 0.517 | 0.489 |
| | B | 92.9 | 0.9 | | |
| | C | 94.1 | 1.3 | | |
| 30 Minutes | | | | | |
| | A | 92.9 | 0.8 | 0.517 | 0.627 |
| | B | 92.4 | 1.3 | | |
| | C | 92.5 | 1.8 | | |
| 1 Hour | | | | | |
| | A | 92.7 | 0.9 | 0.795 | 0.219 |
| | B | 92.9 | 1.3 | | |
| | C | 92.8 | 1.9 | | |
| 2 Hour | | | | | |
| | A | 92.8 | 1.2 | 0.523 | 0.494 |
| | B | 92.9 | 1.4 | | |
| | C | 93.1 | 1.8 | | |
| 3 Hour | | | | | |
| | A | 92.9 | 1.2 | 0.283 | 0.797 |
| | B | 93.1 | 2.3 | | |
| | C | 92.7 | 1.7 | | |
| 4 Hour | | | | | |
| | A | 92.7 | 1.4 | 1.744 | 0.158 |
| | B | 93.8 | 1.5 | | |
| | C | 94.1 | 1.4 | | |
| 5 Hour | | | | | |
| | A | 93.8 | 2.4 | 0.589 | 0.515 |
| | B | 92.9 | 2.3 | | |
| | C | 93.1 | 1.2 | | |
| 6 Hour | | | | | |
| | A | 92.9 | 2.1 | 1.894 | 0.179 |
| | B | 95.7 | 1.5 | | |
| | C | 93.8 | 1.3 | | |
| 8 Hour | | | | | |
| | A | 91.8 | 1.9 | 1.979 | 0.312 |
| | B | 92.9 | 1.3 | | |
| | C | 93.6 | 1.8 | | |
| 12 Hour | | | | | |
| | A | 92.7 | 2.1 | 1.127 | 0.359 |
| | B | 92.1 | 1.2 | | |
| | C | 93.3 | 1.1 | | |
| 16 Hour | | | | | |
| | A | 92.9 | 2.3 | 0.034 | 0.897 |
| | B | 93.6 | 1.2 | | |
| | C | 92.5 | 1.3 | | |
| 24 Hour | | | | | |
| | A | 93.1 | 2.1 | 0.732 | 0.63 |
| | B | 92.9 | 1.2 | | |
| | C | 92.7 | 1.3 | | |

**Table 2c:** Comparison of hemodynamic parameters between three groups at various time intervals (SPO2).

| *SPO2* | *Group* | *Mean* | *S D* | *F* | *P value* |
|---|---|---|---|---|---|
| 5 Minutes | | | | | |
| | A | 97.1 | 0.6 | 0.583 | 0.681 |
| | B | 96.9 | 0.4 | | |
| | C | 97.4 | 0.5 | | |
| 10 Minutes | | | | | |
| | A | 96.8 | 0.5 | 0.778 | 0.351 |
| | B | 97.2 | 0.4 | | |
| | C | 97.4 | 0.5 | | |
| 20 Minutes | | | | | |
| | A | 96.8 | 0.6 | 2.163 | 0.237 |
| | B | 96.9 | 0.5 | | |
| | C | 97.1 | 0.5 | | |
| 30 Minutes | | | | | |
| | A | 97.2 | 0.5 | 0.726 | 0.423 |
| | B | 97.1 | 0.6 | | |
| | C | 97.8 | 0.6 | | |
| 1 Hour | | | | | |
| | A | 97.1 | 0.4 | 0.288 | 0.716 |
| | B | 97.2 | 0.6 | | |
| | C | 96.8 | 0.6 | | |
| 2 Hour | | | | | |
| | A | 97.2 | 0.4 | 1.187 | 0.34 |
| | B | 97.3 | 0.6 | | |
| | C | 97.1 | 0.5 | | |
| 3 Hour | | | | | |
| | A | 97.2 | 0.6 | 2.842 | 0.341 |
| | B | 97.6 | 0.7 | | |
| | C | 97.1 | 0.9 | | |
| 4 Hour | | | | | |
| | A | 98.1 | 0.4 | 2.166 | 0.233 |
| | B | 97.7 | 0.7 | | |
| | C | 98.2 | 0.8 | | |
| 5 Hour | | | | | |
| | A | 96.8 | 0.5 | 2.329 | 0.342 |
| | B | 97.2 | 0.6 | | |
| | C | 97.1 | 0.9 | | |
| 6 Hour | | | | | |
| | A | 98.1 | 0.7 | 1.237 | 0.495 |
| | B | 97.9 | 0.6 | | |
| | C | 97.8 | 0.8 | | |
| 8 Hour | | | | | |
| | A | 97.1 | 0.6 | 1.564 | 0.286 |
| | B | 97.3 | 0.6 | | |
| | C | 98.1 | 0.8 | | |
| 12 Hour | | | | | |
| | A | 97.9 | 0.8 | 2.542 | 0.332 |
| | B | 98.2 | 0.7 | | |
| | C | 98.3 | 0.6 | | |
| 16 Hour | | | | | |
| | A | 97.1 | 0.7 | 1.593 | 0.32 |
| | B | 97.8 | 0.7 | | |
| | C | 97.9 | 0.6 | | |
| 24 Hour | | | | | |
| | A | 97.8 | 0.7 | 0.991 | 0.527 |
| | B | 97.9 | 0.9 | | |
| | C | 98.2 | 0.8 | | |

It was also observed in our study that the onset of sensory block was much faster among group B (bupivacaine with buprenorphine) compared to patients in group A (bupivacaine with normal saline) and C (bupivacaine with clonidine) and the difference was found to be statistically significant. Similarly, the onset of motor block was quicker in group B and A, 3.9 and 4.6 mins respectively, whereas among group C it was much delayed (9.8 mins) and the difference was found to be statistically significant. Complete attainment of sensory block was found to be of almost similar duration among all the three groups, whereas the complete attainment of motor block was much earlier among group A compared to group B and C (17.4 mins vs 19.1 vs 22.6 mins) and this difference in duration was found to be statistically significant. From our study it revealed that the total duration of sensory block is much longer among patients in group B (634.3 mins) compared to A (332.2 mins) and C (459.6 mins) and the difference was found to be statistically significant ($p<.05$), whereas the total duration of motor block was found to be more or less of similar duration among all the three groups (Table 3). As such there were no adverse events reported in any of our study subjects.

## Discussions

There are different types of receptors that mediate nociception in peripheral sensory nerve fibres. The understanding of these receptors is important for administrating different adjuncts along with local anesthetic agents, as these adjuncts would have the potential in prolonging the duration of analgesic effects and reducing the number of systemic analgesics used

and the incidence of side effects. At present there are several adjuncts which were regularly used for prolonging perioperative analgesia, among them opioids found to be very commonly used. The current study was conducted to evaluate the effects of clonidine and buprenorphine being used as analgesic adjuvants along with bupivacaine in supraclavicular block.

**Table 3:** Comparison of time of onset, complete attainment and total duration of sensory and motor block between the three groups.

| *Variables* | *Groups* | *Mean (mins)* | *SD* | *F value* | *P value* |
|---|---|---|---|---|---|
| Onset of sensory block | A | 6.6 | 0.4 | 83.529 | 0 |
| | B | 4.4 | 0.6 | | |
| | C | 5.9 | 0.5 | | |
| Onset of motor block | A | 4.6 | 0.6 | 638.478 | 0 |
| | B | 3.9 | 0.4 | | |
| | C | 9.8 | 0. 7 | | |
| Complete attainment of sensory block | A | 20.2 | 1.5 | 0.592 | 0.638 |
| | B | 20.9 | 2.8 | | |
| | C | 21.8 | 2.9 | | |
| Complete attainment of motor block | A | 17.4 | 1.2 | 20.746 | <0.0001 |
| | B | 19.1 | 1.9 | | |
| | C | 22.6 | 2.3 | | |
| Total duration of sensory block | A | 333.2 | 12.6 | 229.28 | <0.0001 |
| | B | 634.3 | 17.5 | | |
| | C | 459.6 | 68.3 | | |
| Total duration of motor block | A | 318.3 | 10.8 | 2.375 | 0.272 |
| | B | 328.4 | 12.4 | | |
| | C | 313.7 | 12.8 | | |

In early 1990's Cheryl et al. conducted a study comparing ropivacaine and 0.25% bupivacaine for brachial plexus block and concluded that during these types of peripheral blocks patient needs additional analgesia for pain relief [18]. As a result, the use of adjuvants such as opioids, clonidine, verapamil, neostigmine, and tramadol were introduced during brachial plexus block.

In the present study we used 30 ml of 0.3% bupivacaine as anaesthetic agent, as recommended by Gupta et al. in their study, which is based on the theory that selecting the ideal anaesthetic drug concentration is very much important for regulating the drug's volume. A lower concentration of the drug would result in an increase in the anaesthetic agent's volume, which would invariably lead to unfavourable outcomes [8]. According to Franco CD, Vieira et al. study, the ideal dosage for brachial plexus block would be 20 to 30 ml, depending on the drug's concentration. For our patients, we employed 0.3% bupivacaine combined with 1 ml of 300 mcg buprenorphine or 1 ml of 150 mcg clonidine as adjuvants. Haemodynamic parameters which include pulse rate, mean arterial pressure, and SPO2, were tracked for 24 hours in all patients of both the groups and we found no statistically significant difference between the three groups as all the hemodynamic parameters remained stable in the entire follow up period. Studies that were conducted in the recent past produced similar type of results [17-20]. It proves that adding adjuvants like buprenorphine or clonidine in appropriate dosages to the anesthetic agents will not affect the hemodynamic mechanisms.

In the current study, we discovered that the patients in the buprenorphine group had experienced a substantially longer length of sensory block with a significant earlier onset of block compared to the other two groups. Our findings are nearly identical to that of the study Bazin et al.'s study, where he noted a comparable length of analgesia (median 20 hours) following buprenorphine delivery [21]. Another study done by Candido et al. found that the duration of analgesia resulting from the administration of buprenorphine is three times longer than that resulting from the administration of local anaesthetics alone [13, 14]. Following upper extremity surgery, Wajima et al. also discovered a long-lasting and adequate analgesic response when buprenorphine was continuously infused intrabrachially [22]. The high affinity towards mu opioid receptor and high lipid solubility has made buprenorphine for easy penetration through the axonal myelin and nerve membrane, which could be responsible for the prolonged analgesic duration that was observed with the drug. Another contributing factor is its potency, which is 33–35 times more potent than morphine.

Since buprenorphine is a synthetic opioid, its central rather than direct peripheral action is mediated by diffusion or centripetal axonal transport, which is another route for opioid-induced analgesia. However, research by Dahl et al. casting doubt on this notion, they evaluated the effects of morphine given by the perifemoral and extradural routes and they finally concluded that the morphine content in CSF was identical when given in both the routes [23]. This had shown that

opioids had a similar mode of action both in the central and peripheral nervous systems. To substantiate our findings more research on opioids by using different dosages needs to be conducted at different health care settings

## Conclusion

In addition to accelerating the onset of sensory block and extending its length without extending the duration of motor block, adding buprenorphine as an adjuvant to bupivacaine also results in stable haemodynamic parameters without side effects. This indicates that buprenorphine may be a more effective adjuvant for supraclavicular brachial plexus block than clonidine.

## Conflicts of interest

Authors declare no conflicts of interest.

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