Original Article

# Efficacy of multimodal analgesia with perineural buprenorphine or dexmedetomidine for surgeries performed under ultrasound-guided infraclavicular brachial plexus block

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## Abstract

**Background and Aims:** Perineural adjuvants when used as a part of multimodal analgesia (MMA) will maximize the quality and duration of analgesia of the nerve blocks. In the present study, we compared the duration of postoperative analgesia and other block characteristics of two groups of MMA comprising either perineural buprenorphine or dexmedetomidine in the upper limb surgeries performed under ultrasound-guided (US-guided) infraclavicular brachial plexus blocks.

**Material and Methods:** A total of 100 adult patients undergoing elective upper limb orthopedic surgery under US-guided infraclavicular brachial plexus block were randomly divided into two groups. Group I received 150 μg buprenorphine and Group II received 50 μg dexmedetomidine, perineurally added to 30 ml of 0.375% bupivacaine. Both groups also received tramadol 50 mg IV, dexamethasone 4 mg IV, and diclofenac 75 mg infusion as part of MMA. Both groups were compared for the duration of postoperative analgesia, block characteristics, and incidence of adverse effects.

**Results:** The duration of postoperative analgesia was significantly prolonged in Group II (937.6 ± 179.1 min vs 1280.4 ± 288.8 min). The onset of sensory and motor blocks was shorter in Group II ($P < 0.05$). The duration of sensory and motor blocks was significantly prolonged in Group II ($P < 0.05$). The number of rescue analgesics required in the first 24 hours was less in Group II (1.98 ± 0.62 vs 0.8 ± 0.64). Although heart rate and blood pressure levels were lower in Group II, all patients were hemodynamically stable.

**Conclusion:** For surgeries under brachial plexus block, perineural dexmedetomidine when used as a part of MMA provided a prolonged duration of postoperative analgesia and improved block characteristics than perineural buprenorphine.

**Keywords:** Analgesia, buprenorphine, dexmedetomidine, infraclavicular, multimodal

## Introduction

The advent of ultrasound (US) into the practice of anesthesia has made infraclavicular brachial plexus block simple and more effective.[1] However, these advantages are limited by a short duration of action of local anesthetics. Perineural adjuvants have been used to improve the quality of nerve blocks. Nerve blocks with local anesthetics inhibit only neuronal pathways but the humoral inflammatory responses, that occur during surgery, should be blocked by early use of systemic pharmacological therapy, as these biochemical responses may trigger postoperative pain and central sensitization.[2] Hence, we used systemic analgesics along with perineural adjuvants to

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form a part of multimodal analgesia (MMA) by combining different analgesics with different mechanisms of analgesia that act at different sites in the nervous system, resulting in additive or synergistic effects with lowered incidence of adverse effects of individual drugs.[2] There are different studies stating the usefulness of MMA for surgeries that are performed under general anesthesia.[3] In the present study, we have used perineural adjuvants and systemic analgesics, both as a part of MMA for surgeries that are performed under sole brachial plexus block. We compared the two groups of MMA, each group receiving either perineural buprenorphine or dexmedetomidine added to 0.375% bupivacaine along with systemic diclofenac sodium, tramadol, and dexamethasone.

Among opioids, buprenorphine is an agonist-antagonist drug having a substantially longer duration of action and fewer side effects than others.[4] Among α2-agonists, dexmedetomidine has shown to provide a longer duration of analgesia in various regional blocks.[5] Diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID) provides analgesia by inhibiting prostaglandin synthesis.[3] Tramadol, has analgesic as well as antishivering property through its action on μ and serotonin receptors. Dexamethasone the duration of analgesia by promoting the release of anti-inflammatory mediators.[6]

It is hypothesized that perineural dexmedetomidine as a part of MMA may improve postoperative pain control better than perineural buprenorphine. We tested this hypothesis with the primary aim of comparing the duration of postoperative analgesia and the secondary aim of comparing the onset and duration of sensorimotor blocks, number of rescue analgesics required in the first 24 hours and next 24 hours along with hemodynamic and adverse effects of study drugs.

## Material and Methods

This prospective randomized double-blind study was conducted following approval from the hospital ethics committee (BVDUMC and H/Sangli/ IEC/190/16 DATE –23/4/2016). Informed written consent was taken from patients after explaining the procedure in detail. One hundred ASA physical status I or II patients, aged 18–60 years, scheduled for elective orthopedic surgeries of the distal humerus, elbow, forearm, and hand under US-guided infraclavicular brachial plexus block in a tertiary care unit were included in this study. Patients with cardiovascular, respiratory, neurological or renal disease, coagulation abnormalities, pregnancy, and those with known sensitivity to local anesthetics were excluded from the study. The patients were then allocated randomly into two equal groups ($n = 50$ each). The sample size was calculated based on the previous studies.[7,8] At 5% α level of significance and 80% power of the test, the sample size calculated was 49.48 ($n = 50$) patients per group.

Group I received 29 ml of 0.375% bupivacaine plus 150 μg (0.5 ml) of injection buprenorphine diluted to 1 ml with normal saline. Group II received 29 ml of 0.375% bupivacaine plus 50 μg (0.5 ml) of injection dexmedetomidine diluted to 1 ml with normal saline. The total volume of the solution in both groups was 30 ml. Immediately after giving the block, injection tramadol 50 mg IV slowly over 10 min, injection dexamethasone 4 mg IV and infusion of injection diclofenac sodium 75 mg was given as a part of MMA in both groups.

Concealment of randomisation was done by a sealed envelope method. The anesthesiologist performing the block and monitoring the patient as well as one doing data collection was blinded to the study drug.

The patients were kept fasting for 6 hours preoperatively. All patients were instructed about the use of the visual analog scale (VAS) score with zero indicating no pain and ten indicating the worst imaginable pain. In the operating room, monitoring in form of electrocardiography (ECG), pulse oximetry ($SpO_2$), and noninvasive blood pressure (NIBP) was instituted and baseline vitals recorded. An intravenous line was secured with 20 gauge cannula and Ringer's lactate solution infusion was started.

The patients were kept in supine position with the head turned to the opposite side of the block. Under all aseptic precautions, a high-frequency linear probe of 13–6 MHz (Sonosite M turbo US machine) was kept in a parasagittal plane just medial to the coracoid process and inferior to the clavicle. The pulsating axillary artery was visualized. The 5 cm long, short-beveled, 22 gauge nerve stimulator needle was inserted in-plane from cephalic to the caudal direction just inferior to the clavicle. After identifying the artery, the needle was advanced towards the posterior part of the artery and 30 mL of the study drug was injected to achieve a U shaped spread. The time at which injection was given was considered as a zero time of the study and all study parameters were measured from this point.

The sensory block was evaluated by using a modified Hollmen scale[9] as Grade 1 = full sensation, Grade 2 = weak sensation, Grade 3 = sensation under 30%, and Grade 4 = recognized as light touch. Sensory block was assessed at each minute till a complete sensory block (Hollmen scale = 4) was achieved and then every hour till Hollmen scale 1 was achieved. The sensory onset time was taken as the time elapsed between the zero time and the time to achieve Hollmen scale ≥2. The duration of

sensory block was taken as the time elapsed between the zero time and the time to achieve Hollmen scale <4.

The motor block was evaluated by using the modified Bromage scale[10] as zero = no block (normal function with full flexion and extension of the elbow, wrist, and fingers), one = paresis (decreased motor strength with ability to move fingers only), and two = paralysis (complete motor block with inability to move fingers). The findings were recorded at each minute till a complete motor block (modified Bromage scale = 2) was achieved and then every hour till complete recovery of blockade (modified Bromage scale = 0) was achieved. The motor onset time was taken as the time elapsed between the zero time and the time taken to achieve modified Bromage scale 1. The duration of motor block was taken as the time elapsed between the zero time and the time to achieve modified Bromage scale <2.

In the case of insufficient analgesia, supplementation was given with IV midazolam 0.02 mg/kg and IV pentazocine 0.5 mg/kg. If complete sensory and motor blocks were not achieved, 30 min after injection of the study drugs, then it was considered as a failed block and it was decided to convert such cases into general anesthesia. These cases were excluded from the study.

Postoperative pain was assessed by using a VAS score (0–3 = mild pain, 4–7 = moderate pain, and 8–10 = severe pain) every hour for 48 hours. The total duration of postoperative analgesia was taken as the time elapsed between the zero time and the time at which rescue analgesia was demanded by the patient. Injection diclofenac sodium 75 mg IM was given as a rescue analgesic at VAS ≥4 with a maximum dose of 150 mg in 24 hours. The number of rescue analgesics required within the first 24 hours and the next 24 hours was recorded.

All patients were monitored intraoperatively with SpO2, heart rate (HR), ECG, and systolic blood pressure (SBP) every 5 min. In the postoperative period, SBP and HR were recorded every hour. Bradycardia (HR <50) if any was treated with injection atropine 0.6 mg IV. Hypotension (SBP <30% from the baseline or <90 mmHg) was treated with IV crystalloids and injection ephedrine 6 mg IV. Sedation score was tested according to the modified Ramsay sedation scale.[11] All patients were monitored for the side effects such as nausea, vomiting, pruritus, respiratory depression (RR < 8/min). It was decided to treat nausea and vomiting with injection ondansetron 4 mg IV, pruritus with injection promethazine 25 mg IV, and shivering with warm IV fluids and the air warmer.

Statistical analysis was done using SPSS version 22 for Windows (IBM – Chicago). The data were compiled in an excel sheet. Quantitative data were expressed as means ± standard deviation. Z-test (standard error of the difference between two means) was applied for comparing the data. $P$ <0.05 was considered statistically significant.

## Results

No patients were excluded from the study due to failed block. The demographic data is shown in Table 1. The results regarding the characteristics of US-guided infraclavicular brachial plexus blocks are summarized in Table 2. The duration of postoperative analgesia was significantly prolonged in Group II as compared to Group I. The onset of sensory and motor blockade was faster in Group II as compared to Group I. The duration of sensory block was significantly prolonged in Group II. The duration of motor block was significantly longer in Group II. The VAS scores were significantly higher in Group I than in Group II, at 8, 10, 12, 14, 16, 18, and 32 hours [Figure 1]. The number of rescue analgesics required in the first 24 hours and next 24 hours was significantly less in Group II than in Group I [Table 3]. Systolic blood pressure (SBP) levels in Group II were significantly lower than those in Group I, 30 min after the block [$P$ < 0.001] [Figure 2]. HR levels, 60 min after the block were significantly lower in Group II than in Group I [$P$ < 0.00] [Figure 2]. However, there was no incidence of bradycardia and hypotension in either group.

The incidence of side effects was low and not statistically different in the two groups [Table 4]. No patient in either Group developed respiratory depression. Ramsay sedation scores were significantly lower in Group I than in Group II [Table 4].

**Table 1: Demographic data**

| Parameters | Group I ($n$=50) | Group II ($n$=50) |
|---|---|---|
| Age (years) | 42.6±10.2 | 44.2±8.6 |
| Sex (male/female) | 30/20 | 33/17 |
| Weight (kg) | 54.8±7.0 | 55.8±6.5 |
| Height (cm) | 168.2±4.3 | 169.1±3.6 |
| Duration of surgery (min) | 92±24.8 | 93.1±23.4 |

*Values are presented as mean±SD, SD=Standard deviation*

**Table 2: Block characteristics**

| Variables | Group I ($n$=50) | Group II ($n$=50) | $P$ |
|---|---|---|---|
| Onset of sensory block (min) | 4.5±1.6 | 3.9±1.6 | 0.03 |
| Onset of motor block (min) | 6.8±1.6 | 6.0±1.9 | 0.02 |
| Duration of sensory block (min) | 699.4±113.5 | 768.6±128.4 | <0.001 |
| Duration of motor block (min) | 729±110.1 | 790.6±131.8 | 0.01 |
| Duration of postoperative analgesia (min) | 937.6±179.14 | 1280.4±288.8 | <0.001 |

*Values are presented as mean±SD. SD=Standard deviation*

## Discussion

Effective and appropriate pain management requires a proactive approach using a variety of treatment modalities targeting various phases of nociceptive pain processes such as transduction, transmission, perception and descending, and local modulation.[12] Using pre-emptive MMA prior to surgical insult can prevent the release of inflammatory chemicals, increase the threshold for noxious stimulus, decrease postoperative pain, decrease central sensitization, and reduce the risk for development of chronic neuropathic pain. It is proven that, the addition of various opioid and nonopioid adjuvants to local anesthetics in nerve blocks results in better pain control in the postoperative period.[13] Polomano *et al*[12] stated that the likelihood of central sensitization is prevented by completely blocking afferent signals from the surgical incision with the help of systemic pharmacological therapy. We used perineural adjuvants as well as systemic pharmacological agents in our study to improve postoperative analgesia. According to Elvir-Lazo *et al*.,[14] multimodal analgesia regimens are procedure-specific and may include combinations of systemic analgesics (eg., opioids, acetaminophen, nonsteroidal anti-inflammatory drugs, magnesium sulfate, lidocaine, ketamine, dexamethasone, and α2-agonists), neuraxial analgesia, local infiltration, and peripheral nerve blocks. We kept our MMA regimen simple and safe.

Both perineural buprenorphine and dexmedetomidine have shown to potentiate the analgesic efficacy of local anesthetics.[15,16] It is proposed that opioids have local anesthetic-like action on nociceptive neurons, thus explaining their analgesic efficacy in nerve blocks. Dexmedetomidine, a α2-agonist acts on α2 adrenergic receptors in the dorsal horn of spinal cord and locus coeruleus and modulates the release of substance *P* to produce analgesic effects. Along with centrally mediated analgesia, α2B-adrenoceptor mediated vasoconstrictive effects and attenuation of an inflammatory response, it has also a direct action on peripheral nerves.[17]

In a study by Paliwal *et al*.,[18] the duration of analgesia of supraclavicular brachial plexus block was significantly prolonged by perineural buprenorphine (822.8 ± 417.5 min). Sarkar *et al*.[19] found prolonged duration of postoperative analgesia after supraclavicular brachial plexus block in buprenorphine group (698.6 ± 189.5 min) than in the fentanyl group. Singam *et al*.[7] used buprenorphine in supraclavicular brachial plexus block and found significant prolongation of postoperative analgesia (901.3 ± 60.0 min). In our study, the mean duration of analgesia was 937.6 ± 179.1 in the perineural buprenorphine group.

**Table 3: Number of rescue analgesics required**

| Number of RA required in | Group I (*n*=50) | Group II (*n*=50) | *P* |
|---|---|---|---|
| First 24 h | 1.98±0.62 | 0.80±0.64 | *P*<0.001 |
| Next 24 h | 0.74±0.52 | 0.51±0.50 | *P*<0.04 |
| Total 48 h | 2.72±0.78 | 1.31±0.95 | *P*<0.001 |

*Values are presented as mean±SD. SD=Standard deviation, RA=Rescue analgesics*

**Table 4: Side effects**

| Parameters | Group I (*n*=50) | Group II (*n*=50) | *P* |
|---|---|---|---|
| Hypotension | 0 | 0 | - |
| Bradycardia | 0 | 0 | - |
| Nausea/vomiting | 2 | 0 | - |
| Pruritus | 1 | 0 | - |
| Respiratory depression | 0 | 0 | - |
| Ramsay sedation score | 2.52±0.5 | 2.9±0.67 | 0.001 |

*n=Number of patients*

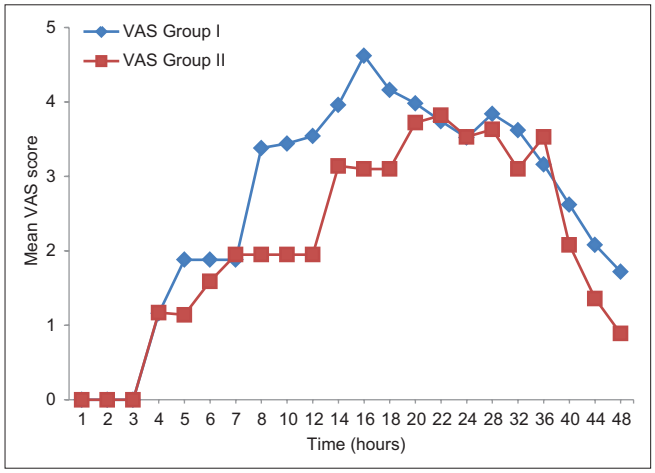


**Figure 1:** Comparison of the mean visual analog scale (VAS) scores

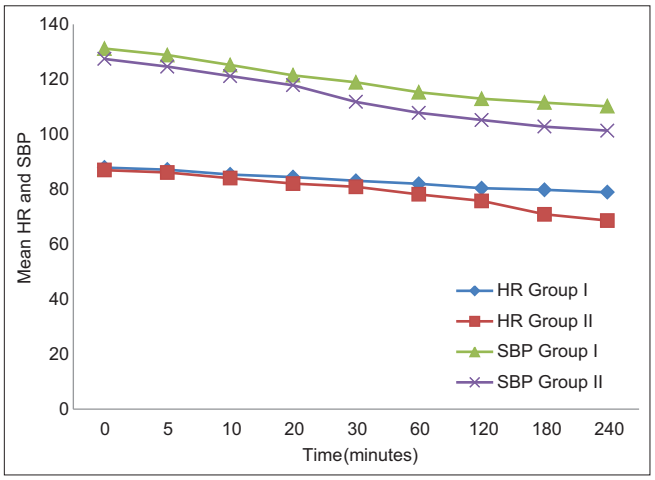


**Figure 2:** Comparison of mean heart rate and mean systolic blood pressure (HR- heart rate per minute, SBP- systolic blood pressure in mmHg)

Esmaoglu *et al*.[20] reported the prolonged duration of postoperative analgesia of axillary brachial plexus block due to addition of dexmedetomidine to levobupivacaine. Ammar *et al*.[16] also found prolongation of the duration of postoperative analgesia after perineural dexmedetomidine in US-guided infraclavicular brachial plexus block. We found an extended duration of postoperative analgesia and reduced requirement of rescue analgesics (RA) in the first 24 hours and next 24 hours in Group II than in Group I. Sivakumar *et al*.[21] also compared these two drugs as adjuvants to bupivacaine for brachial plexus block and reported prolonged duration of postoperative analgesia in dexmedetomidine group.

The sensory and motor block onset times were significantly shortened in the group comprising dexmedetomidine. Zangh *et al*.[22] used dexmedetomidine perineurally for axillary brachial plexus block and found dose-dependent quicker onset of sensory and motor blocks. We also observed significantly longer duration of sensory and motor block in Group II than in Group I. Esmaoglu *et al*.[20] and Agarwal *et al*.[23] also reported a prolonged block duration after perineural dexmedetomidine.

Local anesthetics used neuraxially or perineurally block only neuronal pathways but they do not block the humoral biochemical (inflammatory) responses that occur during surgery. Many neurotransmitters including substance *P* are released locally as well as centrally in response to surgical trauma leading to non-neuronal pain (insensible sensations).[24,25] Drugs such as NSAIDs and dexamethasone, promote the release of anti-inflammatory mediators which the body produces to counteract the inflammatory mediators.[6,26] Dexamethasone is a synthetic glucocorticoid with high potency, long duration of action and low mineralocorticoid activity. Its possible analgesic effect is through the inhibition of white cell aggregation at the endothelial level. Desmet *et al*.[6] stated that dexamethasone increases postoperative analgesia to a similar duration whether given intravenously or perineurally. We used it intravenously as a part of MMA. Tramadol is a centrally acting analgesic causing activation of both opioid and nonopioid systems, which are mainly involved in the inhibition of pain. It enhances inhibitory effects on pain transmission at the spinal level and blocks nociceptive signal transduction both by opioid and monoaminergic mechanisms.[27] We used minimum doses of study drugs based on the concept of MMA[13] so as to maximize the analgesia by synergistic action and to reduce the side effects of individual drugs.

In our study, the mean duration of analgesia was 937.6 min in Group I, which was more than any of the above similar studies. The dose of buprenorphine we used was also lesser than the above studies (150 μg vs. 300 μg). Similarly, we also found a prolonged duration of analgesia (1280.4 min) in Group II. The effectiveness of MMA during surgeries under brachial plexus block will be the probable explanation for prolonged analgesia seen in our study population. However, more studies are required to ascertain the final conclusion. But when the two study groups were compared, Group II population reported prolonged analgesia than Group I, showing more effectivity of α2 agonists than the opioid agonist-antagonist in brachial plexus block.

The incidence of adverse effects noted was very low and was statistically insignificant in either group. The Ramsay sedation score was significantly high in Group II as compared to Group I, though it was always less than three in all the patients in either group. Gurajala *et al*.[28] also reported sedative effects of perineural dexmedetomidine after supraclavicular brachial plexus block. The inhibition of noradrenergic activity via activation of α2 receptors at the locus coeruleus, produces sedation that mimics nonrapid eye-movement sleep.[28]

In the present study, all the study patients were hemodynamically stable, although HR and SBP in Group II were on the lower side than in Group I. But no patient developed clinically significant bradycardia and hypotension. Abdallah *et al*.[5] in his meta-analysis of facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block, reported reversible bradycardia in 7% of brachial plexus block patients. Postsynaptic activation of central α2 adrenoceptors leading to decreased sympathetic activity, might be the reason for decreased heart rate and blood pressure following the use of dexmedetomidine.[8,20]

The confounding variables like co-administration of analgesic drugs and patients with hypertension, cardiac, and renal disease were eliminated by excluding them from the study. Other variables included the history of substance use/abuse, chronic pain conditions, and psychiatric conditions, as these conditions may influence perioperative outcomes. A prospective design, an optimized protocol to reduce the risk of bias, appropriate sample size calculation, use of scoring systems, complete follow-up of all study patients and balanced use of MMA are the strengths of our study.

We did not study the patient's satisfaction score with respect to the discomfort caused by a prolonged motor block in the postoperative period. Single-center design and lack of long-term follow-up for chronic pain are other limitations of our study. Further, multicentric studies are required in this context.

## Conclusion

The MMA group comprising perineural dexmedetomidine is more effective than the one comprising perineural

buprenorphine with respect to the duration of postoperative analgesia, the first 24 hours and next 24 hours of analgesic consumption; and all other block characteristics. Both groups showed hemodynamic stability, although heart rate and systolic blood pressure remained on the lower side in Group II.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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