Original Article

Buprenorphine for postoperative analgesia: Axillary brachial plexus block versus intramuscular administration in a placebo-controlled trial

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Abstract

Background and Aims: Peripheral administration of opioids has been suggested for prolongation of regional analgesia. This prospective, randomized, double-blind placebo-controlled study was undertaken to compare the effect of regional (axillary brachial plexus block [ABPB]) versus intramuscular (IM) buprenorphine (2 μg/kg) in adults.

Material and Methods: Seventy-five adults undergoing upper limb surgery received ABPB with local anaesthetic (15 ml 0.5% bupivacaine, 15 ml 2% lignocaine with adrenaline 1:200,000, 9 ml normal saline [NS]). In addition, regional group RB (n = 25) received buprenorphine 2 μg/kg in ABPB and 1 ml NS IM. Systemic Group SB (n = 25) received 1 ml NS in ABPB and buprenorphine 2 μg/kg IM. Group C (n = 25) received 1 ml NS in ABPB and IM. Onset, duration of sensory and motor block, hemodynamic parameters, sedation score, pain scores using visual analog scale, duration of postoperative analgesia, rescue analgesic (RA) requirement, adverse events, and patient satisfaction were noted.

Results: Demographics, onset and duration of sensory, motor block were similar. RB group had longest duration of analgesia (20.61 ± 1.33 h) compared to SB (10.91 ± 0.90 h) and control group (5.86 ± 0.57 h) (P < 0.05 RB vs. SB/C and SB vs. C). RA requirement was highest in the control group and least in RB group (P = 0.000 RB vs. SB/C and SB vs. C). SB group had a maximum number of side effects (P = 0.041, SB vs. RB/C). Patient satisfaction was highest with group RB (P < 0.05 RB vs. SB/C, and P = 0.06 SB vs. C).

Conclusion: Buprenorphine 2 μg/kg in axillary plexus block provides significantly prolonged analgesia with less RA requirement and greater patient satisfaction compared to IM administration. This is highly suggestive of action on peripheral opioid receptors.

Key words: Axillary brachial plexus block, buprenorphine, postoperative analgesia

Introduction

Opiates are widely known to have an antinociceptive effect at central and/or spinal cord level. However, neurophysiologic evidence has supported the concept of opioid antinociception by activation of peripheral opioid receptors.[1] Animal studies have also supported the evidence that primary afferent neurons and immune cells have a significant number of opiate receptor sites on their central processes.[2] If, peripheral opioid administration improves regional anesthesia without centrally mediated side effects, it would be useful in clinical practice. The results of earlier studies using opioids in brachial plexus block were inconclusive.[3] Some of the studies did not have systemic control group and few did not have a placebo group.[4,5] In the majority of the studies with buprenorphine as a local anesthetic (LA) adjuvant, either a fixed dose of 300 μg or 3 μg/kg has been used.[6-9] Very few studies[10] till date have been done to evaluate the effect of the lower dose of buprenorphine (2 μg/kg) as an LA adjuvant. Hence, this placebo-controlled trial was undertaken to compare the effect of regional (axillary brachial plexus block [ABPB]) versus intramuscular (IM) administration of buprenorphine (2 μg/kg) in adults undergoing upper limb surgeries.

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Material and Methods

Following approval from the Departmental Review Board, a prospective, randomized, double-blind, controlled study was

conducted in 75 adult patients in age group of 18-60 years, body weight 40-80 kg, American Society of Anesthesiologists grade I, II, scheduled for upper limb surgery under ABPB. Upper limb surgeries like open reduction internal fixation for fracture radius, ulna or both, tendon repair, carpal tunnel release, and debridement were selected for the study. Patients having relative contraindications to axillary block (like allergy, coagulation disorder), systemic disorders (epilepsy, deranged renal, liver function tests) were excluded from the study. Informed written consent was obtained from each patient.

Patients were randomly allocated in three groups. Patients in regional group RB ($n = 25$) received 40 ml of LA solution containing 15 ml 0.5% bupivacaine, 15 ml 2% lignocaine with adrenaline 1:200000, 9 ml normal saline (NS) plus 2 μg/kg buprenorphine diluted to 1 ml NS for axillary block and IM 1 ml NS. Systemic group SB ($n = 25$) received LA only block and IM 2 μg/kg buprenorphine diluted to 1 ml NS. Control group C ($n = 25$) received LA only block and IM 1 ml NS.

Computer-generated randomization chart was prepared. Allocation concealment was done using sequentially numbered, sealed, opaque envelopes. X anesthetist opened the sealed envelope and prepared drugs in two syringes A and B. Syringe A and B either contained 1 ml of 2 μg/kg buprenorphine or 1 ml NS depending on the allotment. Syringe A drug was added to LA solution for axillary block. Syringe B drug was injected IM in opposite gluteal region. Y anesthetist performing the block was unaware of the drug in two syringes and continued monitoring for 36 h.

American Society of Anesthesiologists standard monitoring was established. Intravenous access was secured. The arm to be blocked was abducted to 90°, externally rotated and hand supinated. Under aseptic precautions, axillary block was performed with the technique of Lavoie *et al*.[11] using a 22-gauge insulated needle and a nerve stimulator. After production of characteristic motor response by stimulation of musculocutaneous nerve and one of the three (median, ulnar or radial) nerves at 0.5 mA, LA solution including study drug was injected. Intercostobrachial nerve was blocked by injecting 5 ml LA solution subcutaneously in an arc from biceps to triceps along axillary surface of the arm. Onset time for sensory and motor block was taken as time between injection and loss of sensation in one particular nerve distribution by pinprick test and loss of flexion/extension movement in hand or arm against gravity, respectively.

A three-level scale was used to grade the quality of sensory block: 0 – sharp pain, 1 – only touch but no prick, 2 – not even touch. Quality of motor block of upper extremity was graded on a four-level scale: 0 – full flexion/extension movement in hand and arm against resistance, 1 – movement against gravity but not against resistance, 2 – flicker of movement in hand but not in arm, and 3 – no movement (complete motor block). Both sensory and motor components of the block were assessed every 5 min for 30 min and thereafter on completion of surgery in postoperative care unit. A complete block was defined as one associated with grade 2 sensory anesthesia and grade 3 motor block and only these patients were included for further study. Patient with sensory block of grade 0, 1 and motor block of grade 0, 1, and 2 were considered to have incomplete block and hence were excluded from further analysis.

Duration of sensory block was considered as time from complete sensory block to return of paresthesia. Duration of motor block was considered from time between complete motor block to restoration of the full hand and wrist mobility.

Hemodynamic parameters (heart rate, systolic blood pressure), respiratory rate, and SpO_2 were monitored every 10 min intraoperatively. Postoperatively, same parameters except SpO_2 were monitored every hourly for first 8 h.

Pain assessment was done using visual analog score (VAS) scale (0 – no pain to 10 – worst pain). Time between block administration and onset of pain (VAS ≥ 4) was taken as the duration of analgesia. VAS assessment was done every hour for first 8 h then 2 hourly for 24 h and 4 hourly up to 36 h in awake patients. However, patients who were fast asleep were not disturbed for the assessment. Rescue analgesia (RA) in the form of injection diclofenac 75 mg IM was given at VAS ≥ 4. Next dose of RA was repeated after 8 h if required. Requirement of RA over 36 h was noted.

Sedation score was graded on a simple scale as: 0 – fully alert; 1 – alert, quiet, obeys verbal commands; 2 – sleepy but prompt response to verbal commands; 3 – sleepy but prompt response to light glabellar tap; 4 – sleepy, responding only to firm glabellar tap. Sedation score was assessed at every hour for first 12 h. Adverse effects like hypotension, bradycardia, nausea, vomiting, respiratory depression, pruritus, urinary retention were noted. At the end of 36 h, patient satisfaction for pain relief was graded as: Excellent, good, fair, poor.

Statistical analysis

Sample size was calculated based on duration of postoperative analgesia in Candido *et al*.'s study.[6] With 5% alpha error and keeping 20% beta error, the sample size of 20 patients per group was required. Hence, we used a sample of 25 patients in each group. Statistical analysis was performed using SPSS (version 12.0; SPSS, Inc., Chicago, IL, USA) software.

The mean and standard deviation were calculated for variables such as demographics, onset and duration of sensory/motor block and duration of analgesia. They were analyzed using analysis of variance (ANOVA) followed by unpaired *t*-test. RA requirement and patient satisfaction were compared using Chi-square/Fisher's exact test. A $P < 0.05$ was considered as statistically significant.

Results

Initially, 75 patients were enrolled in the study. Eight patients were excluded later because of lack of complete block (3 in RB, 2 in SB and 3 in C group). All three groups were comparable in demographic parameters [Table 1]. Onset and duration of sensory and motor block was similar in three groups [Table 2]. Hemodynamic parameters (peak rise in pulse rate and blood pressure) were corresponding with VAS scores. Both buprenorphine groups had higher sedation scores compared to the control group ($P < 0.05$, RB/SB vs. C) in first 7 h [Figure 1].

A graph of VAS score at different time points has been shown in Figure 2. When the VAS score reached value of 4, the patient received first RA, and was subsequently excluded from further analysis. All patients in group C, SB, and RB received RAs by 7, 12, and 22 h, respectively. Hence, from those time points, VAS score of 4 is extrapolated in Figure 2. VAS scores were higher in the control group versus both buprenorphine groups. SB group had significantly higher VAS scores compared to RB group [Figure 2].

Duration of analgesia was the highest in RB (20.61 ± 1.33 h), medium in SB (10.91 ± 0.90) and least in control group (5.86 ± 0.57 h) ($P < 0.05$ for RB vs. SB/C and SB vs. C) [Table 2].

RA requirement was the highest in the control group and least in RB group ($P < 0.05$ for RB vs. SB/C and SB vs. C) [Figure 3]. In group RB and C, one patient had nausea and rest all were free from any side effects. Whereas, in SB group 3 patients had nausea, 4 had vomiting, and 1 had urinary retention (Group SB vs. RB/C, $P = 0.041$) [Table 2]. Overall, patient satisfaction for pain relief was better in RB as compared to SB and control groups ($P < 0.05$, RB vs. SB/C, $P = 0.06$, SB vs. C) [Figure 4].

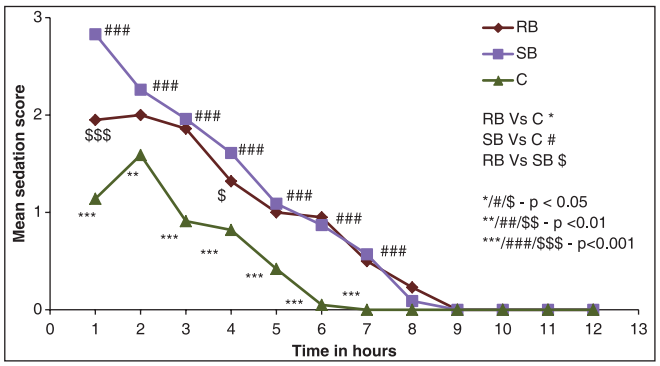

Figure 1: Mean sedation score in three groups

Discussion

Brachial plexus block with LAs has been used for upper limb surgeries. Additives such as adrenaline, α-2 agonists, neostigmine, and opioids have been investigated for prolongation of analgesia. Initial experimental studies by Field *et al.*[2] on rats have demonstrated the presence of opioid receptors on primary afferent neurons and peripheral sensory nerve fibers by immunocytochemical methods. Although the presence of peripheral receptors in human has been well documented, their mechanism of action remains unclear.[1] The proposed antinociceptive actions of peripherally administered opioids include a nonspecific, LA like effect. This includes a decrease

Table 1: Demographic data

Parameter	Group			*P*
	RB (*n* = 22)	SB (*n* = 23)	Control (*n* = 22)	
Age (years)*	28.36±4.45	28.22±3.41	26.27±3.58	0.138
Sex (male:female)†	11:11	10:13	13:9	0.576
Weight (kg)*	57.64±4.68	57.17±4.09	55.41±4.40	0.215
Duration of surgery (h)*	2.15±0.48	1.99±0.50	2.01±0.37	0.459
Tourniquet time (h)*	0.92±0.24	0.93±0.24	0.99±0.17	0.539

**ANOVA test, †Chi-square, P > 0.05 not significant, RB = Regional buprenorphine, SB = Systemic buprenorphine, ANOVA = Analysis of variance*

Table 2: Onset, duration of block, duration of postoperative analgesia and adverse effects

Time	Groups			*P*
	RB (*n* = 22)	SB (*n* = 23)	Control (*n* = 22)	
Onset of sensory block (min)	3.76±0.53	3.83±0.38	3.60±0.52	0.285
Onset of motor block (min)	6.85±0.84	7.35±0.77	7.05±0.98	0.165
Duration of sensory block (h)	5.40±0.49	5.44±0.45	5.21±0.43	0.214
Duration of motor block (h)	4.74±0.50	4.85±0.45	4.65±0.43	0.382
Duration of analgesia (h)	20.61±1.33	10.91±0.90	5.86±0.57	<0.05**
Adverse effects				0.041 for SB versus RB/C
Nausea	1	3	1	
Vomiting	0	4	0	
Urinary retention	0	1	0	

*Onset, duration of block, duration of postoperative analgesia expressed as mean ± SD. Adverse effects are mentioned as number of patients, SD = Standard deviation, RB = Regional buprenorphine, SB = Systemic buprenorphine, **0.000 (as p < 0.001)*

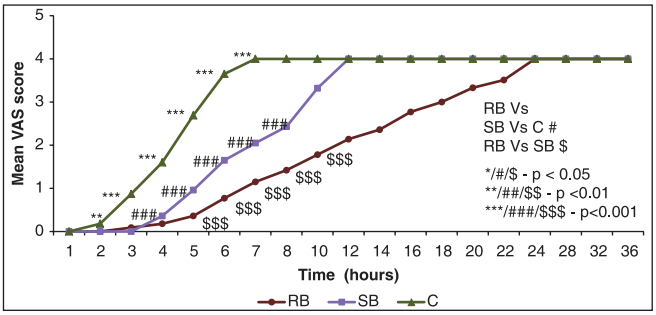

Figure 2: Comparison of mean visual analog score in three groups

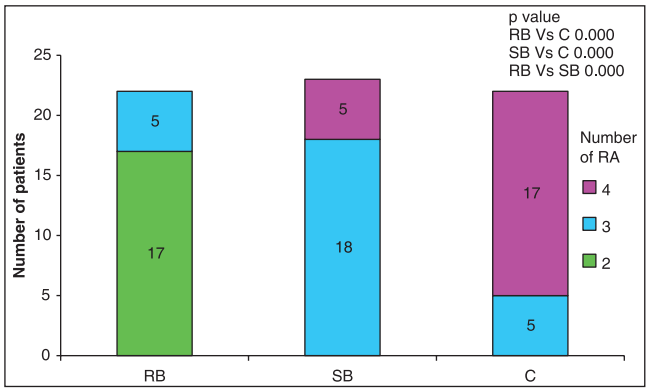

Figure 3: Rescue analgesic dose requirement in three groups

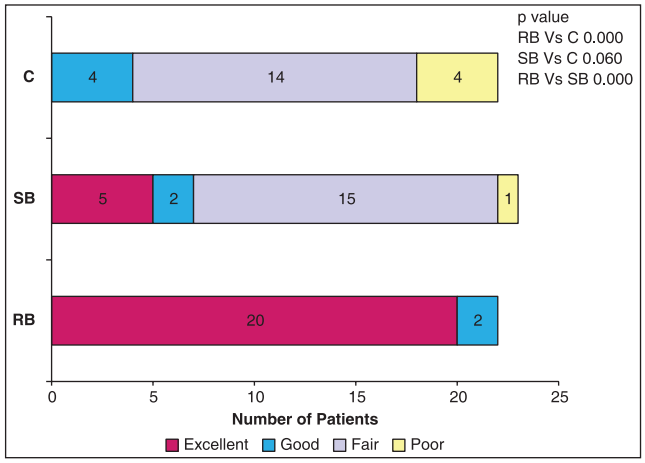

Figure 4: Patient satisfaction level

in K^+ conduction and an increase in Ca^{++} conduction in the cell body of sensory neuron. This reduces excitability of the nociceptive neuron. Opioids also inhibit the release of excitatory neurotransmitter substance P from the peripheral sensory nerve endings. They may have central action caused by centripetal movement via opioid binding proteins from periphery to the dorsal horn.

It is worth administering opioid in the plexus block only if it provides better and longer duration analgesia with lesser side effects compared to systemically administered drug. Murphy *et al.*[3] reported a systematic review of studies from 1966 to December 1999 of analgesic adjuncts for brachial plexus block. Of 10 studies using opioids, six were supportive, and four were negative. Of four studies using a systemic control, two were supportive, and two were negative. They concluded that there is minimal evidence for any analgesic benefit of using opioid analgesics in brachial plexus block over systemic administration. In addition, there appeared to be no advantage for reduced adverse effects by the peripheral administration of opioid analgesics. However, one interesting finding was that their review included two supportive studies using buprenorphine (3 μg/kg) by Viel *et al.*[4] and Bazin *et al.*,[12] with duration of analgesia of 35.05 ± 1.95 and 20 (14-34) h, respectively.

Salient features of buprenorphine namely, long duration of action, lipophilic nature, high affinity for μ-receptor as compared to other opioids and ceiling effect on respiratory depression has further stimulated the research in this area. Moreover, it is freely available and cost effective.

From 2001 onward, eight studies[5-10,13,14] have reported significantly long duration of analgesia using buprenorphine in brachial plexus block. However, only three[6,10,13] out of eight studies had systemic control group. Rest five studies[5,7-9,14] had placebo control group where plain LAs were used for the block. In 2008, Jadon *et al.*[13] studied the effect of the addition of 3 μg/kg buprenorphine to 0.3% bupivacaine in subclavian perivascular block. Though this study had a systemic opioid control group, there was no placebo control group, and site of block was in close proximity to the central neuraxis. We thought it is essential to have study group, systemic control, and placebo, that is, only LA plexus block group. As the type of approach for the block and LA varied in all studies, one cannot presume the duration of analgesia in pure LA block. Only two studies (Candido *et al.*, 2002,[6] Behr *et al.*, 2012[10]) so far have been done with all three groups. Our study is an attempt to fill this lacuna in the existing literature. Our study showed significantly longer duration of analgesia and reduced requirement of RAs with buprenorphine addition in axillary plexus block compared to IM administration. This is an additional evidence supporting peripherally mediated analgesic action.

In five out of eight above-mentioned studies, fixed dose of buprenorphine was used. In four studies,[5-7,14] 300 μg and in one study[10] 150 μg of buprenorphine was used. In three[8,9,13] out of eight above-mentioned studies, 3 μg/kg buprenorphine was used. Our earlier unpublished experience of using lower doses of buprenorphine, as an adjuvant to spinal anesthesia made us utilize its excellent long lasting analgesic effect even at lower doses. Hence, we decided to use lower doses of buprenorphine (2 μg/kg) as an LA adjuvant in ABPB,

which may be beneficial in ambulatory surgeries. In our study buprenorphine (2 μg/kg) as LA adjuvant in ABPB provided 20.61 ± 1.33 h of analgesia. This is beneficial for safe discharge after day care surgeries. In spite of lower dosages, our study had similar results to that of study by Candido *et al*.,[6] using buprenorphine 300 μg. Mean duration of analgesia in their study was 22.3 ± 3.1 h with regional buprenorphine as compared to IM buprenorphine (12.5 ± 1.5 h).

Buprenorphine via axillary plexus block can act by: (1) Systemic absorption, (2) spread to central neuraxis, and (3) direct action on peripheral opioid receptors on plexus nerves. In our study regionally administered buprenrphine provided 20.61 ± 1.33 h of analgesia compared to 10.91 ± 0.90 h of analgesia by IM route. This makes systemic absorption as unlikely mechanism. Spread to central neuraxis is also unlikely mechanism as brachial plexus was blocked by axillary approach, a distant site from spinal cord. Furthermore, the drug selected for trial – buprenorphine, is lipophilic and has high affinity for μ-receptor and hence unlikely to get transported to spinal cord. Hence, most likely site of action is at peripheral opioid receptors on plexus nerves.

In a study by Candido *et al*.,[6] incidence of vomiting in the systemic group was 25% compared to 5% in the regional group. Jadon *et al*.[13] study had a similar incidence of vomiting in both groups. In our study, 17.4% of patients had vomiting in the systemic group compared to none in the regional group. This again emphasizes the importance of regional administration of buprenorphine.

In our study, addition of buprenorphine did not prolong the onset and duration of sensory and motor block which is comparable to the study done by Dixit *et al*.[9] in 2013.

Although the actual neurophysiochemical mechanism is speculative, the present study provides the convincing evidence of benefits of adding buprenorphine 2 μg/kg to LA solutions for upper extremity blocks in day care surgeries. Further work is needed to define the mechanism of peripheral action of opioids. A dose-finding study with lower doses for buprenorphine in axillary block may be done to determine maximum beneficial effects at lower doses.

Conclusion

Buprenorphine 2 μg/kg in axillary plexus block provides significantly prolonged analgesia with less RA requirement and greater patient satisfaction compared to IM administration.

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