Original Article

A PROSPECTIVE, RANDOMIZED, DOUBLE BLINDED COMPARATIVE STUDY BETWEEN 0.5% BUPIVACAINE AND 0.5% BUPIVACAINE WITH PENTAZOCINE AS AN ADJUVANT IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK FOR POST OPERATIVE ANALGESIA IN UPPER LIMB SURGERY

(Pentazocine as adjuvant in brachial plexus block)

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Summary

Introduction: *In upper limb surgery supraclavicular brachial plexus (SCBP) block with 0.5% bupivacaine is commonly used for anesthesia. To increase the duration of sensory block opioids are used along with bupivacaine, but data on the effect of pentazocine as adjuvant with bupivacaine in SCBP block is still lacking. The study aimed to compare the duration of postoperative analgesia, sensory and motor block between 0.5% bupivacaine and 0.5% bupivacaine with pentazocine as an adjuvant in SCBP.* ***Methods:*** *The study was conducted on 60 consenting patients, posted for upper limb orthopedic surgery involving the forearm under SCBP block. Patients were randomly divided into two groups. Group B received 19 ml of 0.5 % bupivacaine with 1 ml of normal saline; Group BP received 19 ml of 0.5 % bupivacaine with 1 ml pentazocine (30 mg). Block characteristics, duration of postoperative analgesia, and side effects if any were recorded. Statistical analysis was done using the student t-test and Chi-square test for continuous and categorical variables respectively.* ***Results:*** *The onset of sensory (11.47 ± 1.57 vs. 16.8 ± 2.23 min) and motor (8.17 ± 1.14 vs. 13.9 ± 2.44 min) block was significantly faster in the BP group. Duration of sensory (392.33 ± 9.92 vs. 357.2 ± 8.76 min) and motor (379.27 ± 9.28 vs. 347.27 ± 9.13 min) block was also prolonged in group BP (p < 0.0001). Duration of postoperative analgesia was more (p < 0.0001) in the BP group (407.43 ± 10.46 vs 367.3 ± 8.74min).* ***Conclusion:*** *Pentazocine as an adjuvant with bupivacaine in SCBP block provides faster onset, prolonged duration of the block, and postoperative analgesia*

Key words: *Analgesia; brachial plexus block; bupivacaine; pentazocine*

Introduction

Both intra-operative and post-operative pain is a real concern in anesthesia. Intraoperative pain relief is mandatory for stable hemodynamic and smooth surgical procedure whereas postoperative pain relief accelerates early recovery of the patient. In upper limb surgery, supraclavicular brachial plexus (SCBP) block with a long-acting local anesthetic (bupivacaine, ropivacaine, and levobupivacaine) is a widely used method[1].

However, to increase the duration of the sensory blockade and postoperative analgesia, opioids (morphine, fentanyl, buprenorphine, tramadol), alpha 2 agonists (clonidine and dexmedetomidine), dexamethasone, magnesium, and epinephrine are used as an adjuvant with 0.5% bupivacaine, 0.5% levobupivacaine and 0.75% of ropivacaine[2]. The addition of an adjuvant to local anesthetic not only prolongs the duration but also reduces the dose of local anesthetic leading to less chance of systemic toxicity[3].

Pentazocine, a synthetic agonist-antagonist opioid, acts as a weak antagonist or a partial agonist at μ - opioid receptors. Analgesia is produced mainly through interaction with the kappa (k1) receptor[4]. Pentazocine has been used as sole anesthetic or adjuvant to 0.5% bupivacaine via the spinal and epidural route in the dose range of 0.8 mg to

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60 mg without any adverse effects and effectively produced sensory block, motor block, and analgesia[5-8]. In the present study we planned to use pentazocine as an adjuvant to 0.5% bupivacaine in the SCBP block.

An alternate hypothesis was accepted for the present study assuming that a significant difference would be observed by adding 30 mg pentazocine to 0.5% bupivacaine for SCBP block regarding the duration of block and postoperative analgesia depending on the observations made by the pilot study.

Objective

The primary objective of the study was to compare the duration of postoperative analgesia as well as the duration of sensory and motor block. Comparison of sedation and the onset of sensory and motor block were secondary objectives.

Methods

After obtaining institutional ethics committee clearance and successful registration in the clinical trials registry of India (CTRI/2020/07/026494 dated 10.07.2020), this prospective, randomized, double-blinded, analytical study was conducted in orthopedic operation theatre of a tertiary care hospital from August 2020. to July 2021. with 60 ASA I and II patients of either sex, aged between 18-60 years admitted for elective upper limb orthopedic surgery involving the forearm under supraclavicular brachial plexus (SCBP) block. All the patients were included in the study after written informed consent. Patients having any contraindications to regional anesthesia (coagulopathy, infection in the supraclavicular region or obese patient (body mass index >30 kg/m^2)) were excluded from the study. Patients who have a history of severe systemic disease, neuromuscular, psychological disorders, or allergy to the study drugs were also excluded from the study. Patients with a history of chronic drug, alcohol, or analgesic abuse and pregnant patients were not included in the present study. Patients who required supplementary analgesic or anesthetic intra-operatively or converted to general anesthesia were also excluded from the study.

As there is no previous study on pentazocine as an adjuvant to 0.5% bupivacaine in supraclavicular brachial plexus block, a pilot study was done by an anesthesiologist (not related to this study) on 30 patients (15 patients in each group)[9]. It was observed that 80% (12 patients) of the patients who received pentazocine as an adjuvant to 0.5% bupivacaine had effective pain relief for 6 hours, compared to 40% (6 patients) when normal saline was used as an adjuvant.

Accepting an alpha error of 5% (CI 95%), power of the study of 80%, and considering the effect to be one-tailed, we get a sample size of 48 patients to be divided into two groups (24 patients in each group) using OpenEpi version 3.01 software (2013 version). To compensate for losses and dropouts particularly due to the administration of intraoperative opioids or conversion to general anesthesia, 30 patients were included in each group.

Patients were randomly divided into two groups B (bupivacaine group) and BP (bupivacaine with preservative-free pentazocine group). Group B received 19 ml of 0.5 % bupivacaine with 1 ml of normal saline; Group BP received 19 ml of 0.5 % bupivacaine added with 1 ml of preservative-free pentazocine (30 mg/ml). SCBP blocks were performed with the help of a nerve locator.

After the patient was properly explained the technique, positioning was done and approximately 1–1.5 cm above the midpoint of the clavicle 2 ml of 2% Xylocaine was infiltrated and a mark was made. A 22-gauge 5 cm, insulated, Stimuplex® A needle with a stimulation frequency of 1 Hz was used. Output current was initially set at 2 mA and then gradually decreased to < 0.5 mA. With persistent motor response in the forearm and hand at 0.5 mA, the study drug was injected slowly after negative aspiration. The anesthesiologist who performed the SCBP block and maintained the record of different parameters was unaware of the group allocation. Randomization by computer-generated random number table and sealed envelope technique was used. Drug preparation was done by an anesthesiologist not involved in the study outside the OT, depending on the group to which the number in the envelope belongs.

The sensory block was evaluated using alcohol swabs every two min after administration of the study drug in the distribution of musculocutaneous (anterolateral forearm), median (lateral 2/3rd

of hand and the tips of digits 1-4), ulnar (palm and medial side of hand and digits 3-5), and radial (posterior aspect of the lateral forearm and wrist; posterior arm) nerve. Time for the onset of sensory block was defined as the time from completion of injection (Time 0) to the time when less sensation to cold swab began to be detected in the distribution of any one of the major nerves on the operating limb compared to the contralateral side.

The block was failed if the sensory block was found to be inadequate in any of the nerve distribution after 30 min of drug administration and such patients were then excluded from the study and considered for general anesthesia or supplemental intravenous analgesic or anesthetic. All the patients were given moist O_2 4L/min via nasal prong throughout the intra-operative period.

Motor block was assessed for four nerves (flexion of the elbow, thumb adduction, thumb abduction, and thumb opposition). Motor blockade was assessed on a 3-point scale: 0 = no block (full extension and flexion of elbow, wrist, and fingers); 1 = reduced motor power with the finger movements; and 2 = complete motor block with no finger movement[10]. Time from completion of drug administration to the development of motor block score ≥ 1 was noted as the onset of motor block and score 2 was recorded as the time for complete motor block.

Sensory and motor block were assessed every 15-minute interval after the end of surgery along with Visual Analogue Scale (VAS) score. Duration of sensory block was measured from the onset of sensory block to complete return of sensation to cold swab in the distribution of all four nerves in the operating limb. Duration of motor block was defined as the time of attaining score 1 before surgery to complete recovery of motor power of the hand and fingers, i.e., score 0 after surgery.

After the patient complained of a VAS score ≥ 4 (which was explained previously to the patients) in the postoperative ward, paracetamol 1g I.V. was given (not exceeding 3g/24h). If the patient still complained of pain a half hour after paracetamol administration, pentazocine 30 mg was administered intramuscularly. Duration of postoperative analgesia (time interval between the onset of sensory block to the time of administration of 1st analgesic) was also noted.

Heart rate, intraoperative systolic, diastolic, and mean arterial blood pressures at 5 minutes time intervals up to 2 hours (after drug administration). Electrocardiogram (ECG), respiratory rate (RR), and oxygen saturation (SpO_2) were continuously monitored throughout the period. Side effects such as hypotension, bradycardia, nausea, vomiting, pruritus, shivering, and respiratory depression (RR less than 8 per minute) were recorded till 6 hours postoperatively[11]. Sedation was assessed using Ramsay's sedation score every two hours postoperatively. (Score 1- Anxious, agitated, or restless, 2 - Cooperative, oriented, and tranquil, 3 - Responds to command, 4 - Asleep but has a brisk response to a light glabellar tap or loud auditory stimulus, 5 - Asleep and has a sluggish response to a light glabellar tap or loud auditory stimulus, 6 - Asleep no response)[12].

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as percentages. Results were analyzed by Mann-Whitney U-test for nonparametric and unpaired Student's t-test for parametric data. For categorical data, the Chi-square test and Fischer's exact test were used as appropriate. A p-value < 0.05 was considered statistically significant. Data analysis was done by Statistical Package for the Social Science or SPSS® software released in 2015, (Version 23.0. Armonk, NY: IBM Corp.).

Results

74 patients were enrolled in the study. Six patients refused to participate in the study and eight patients did not meet the inclusion criteria so, 60 patients were finally allocated into two study groups by simple randomization (Figure 1).

Differences in age, gender, and weight in both groups B and BP were not significant in our study. The duration of surgery and the ASA physical status of the patients were also comparable between the groups (Table 1).

The onset of motor and sensory block was significantly faster in patients who received pentazocine in brachial plexus block (p < 0.0001). Duration of sensory and motor block was also significantly prolonged when pentazocine was administered with bupivacaine in the brachial plexus block (p < 0.0001). Total analgesia duration was found to be
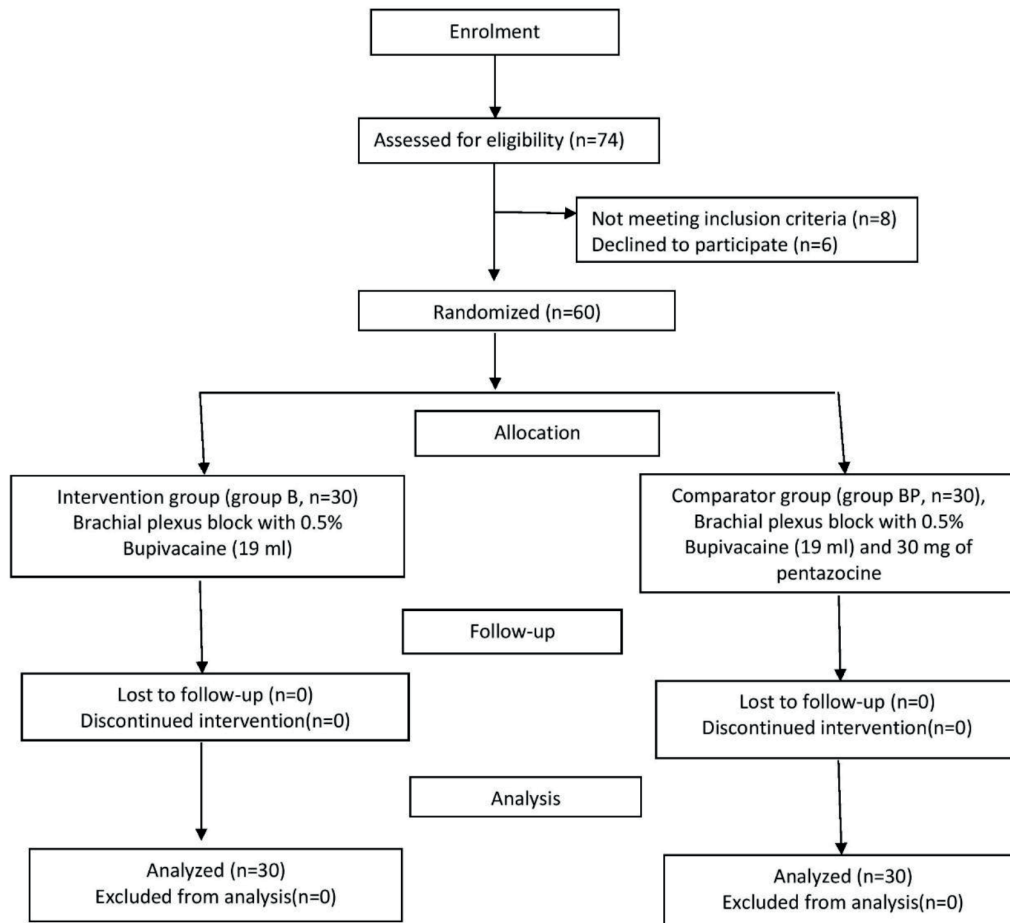
Figure 1: CONSORT 2010 STUDY FLOW CHART

Table 1: Demographic Profile

	Group B (n=30)	Group BP (n=30)	*P* value
Age (yrs)	39.37 ±11.35	39.17 ± 4.96	0.932 #
Sex (M/F)	17/13	16/14	1*
ASA status (I/II)	25/5	27/3	1*
Weight (kg)	64.2 ± 5.98	66.1 ± 6.38	0.300 #
Duration of surgery (min)	76.5 ± 10.66	76.87 ± 10.92	1#

ASA: American Society of Anesthesiologists, *Chi-Squared Test #Unpaired Student's t-test

Table 2: Block characteristics and analgesia

Duration in min	Group B (n=30)	Group BP (n=30)	*P* value
Onset of sensory block	16.8 ± 2.23	11.47± 1.57*	<0.0001#
Onset of motor block	13.9 ± 2.44	8.17 ± 1.14*	<0.0001#
Duration of sensory block	357.2 ± 8.76	392.33 ± 9.92*	<0.0001#
Duration of motor block	347.27 ± 9.13	379.27± 9.28*	<0.0001#
Total analgesia duration	367.3 ± 8.74	407.43 ±10.46*	<0.0001#

#Unpaired Student's t-test

significantly higher in group BP than in group B (p < 0.0001) (Table 2).

Hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure up to 2 hours (after drug administration) were compared in both groups intraoperatively. Intraoperative hemodynamic parameters were found not significant between the groups (p > 0.060 in all instances). Intraoperative oxygen saturation level was also found insignificant.

Intraoperative Ramsay sedation score was higher in patients who received pentazocine (4.5 ± 0.57) compared to those who did not (1.57 ± 0.57) (p < 0.0001)(Table 3).

In the current study, no patient had any significant adverse effects (pneumothorax, post-operative vomiting, oxygen saturation < 90% at any time point, bradycardia, signs of local anesthetic toxicity, neurological complication, etc.). But a total of 4 patients (2 patients in each group) complained about mild nausea at different time points which subsided without any medications.

Discussion

Though ropivacaine and levobupivacaine have lower cardiac toxicity, clinically no difference was observed in the previous studies regarding adverse

Table 3: Highest Ramsay sedation score

	Group B (Mean±SD)	Group BP (Mean±SD)	P – value
Ramsay Sedation Score	1.57 ± 0.57	4.5 ± 0.57*	<0.0001[@]

@ Mann-Whitney U-test

effects of bupivacaine, levobupivacaine, and ropivacaine[13-15]. In the present study we have used bupivacaine as it is widely available and relatively cheaper compared to other long-acting local anesthetics.

Several pure agonist opioids like morphine, fentanyl, and sufentanil have been used as adjuvants to local anesthetics for brachial plexus block with varying degrees of success[3,16].

The mechanism of action of opioids in peripheral blocks is still undefined. Evidence of the existence of peripheral opioid receptors is present. When an opioid is used along with local anesthetic in peripheral nerve block, prolongation of analgesia is probably due to axonal diffusion (e.g. through the neuronal sheath of nerves) into epidural or subarachnoid space and binding with opioid receptors in the dorsal root of the spinal cord. It can also be due to systemic absorption of opioids[17].

Opioids belonging to mixed agonist-antagonists like butorphanol and nalbuphine have also been used as adjuvants to local anesthetics in several studies with favorable results[18-24]. Pentazocine belongs to a mixed agonist-antagonist opioid-like nalbuphine and butorphanol[4,25] but no study to

date has used pentazocine as an adjuvant to local anesthetic in brachial plexus block.

In SCBP block, previous studies have used nalbuphine as adjuvant in the dose range of 5-10 mg[18-20], whereas butorphanol has been used in the dose range of 1-2 mg[22-24]. When used parenterally, 30 mg of pentazocine is equivalent to 10 mg of morphine which is again equivalent to 10 mg of nalbuphine[4,25] whereas 1 mg butorphanol is equivalent to 30 mg pentazocine[26]. In the present study, an equipotent dose of pentazocine compared to nalbuphine and butorphanol has been used.

Pentazocine has been used in neuraxial block (spinal and epidural) in higher doses (60 mg in one study and 1.5 mg/kg in another) without any incidence of neuropathy, so we consider it to be safe when used in peripheral nerve block[5,6].

Studies with morphine[27], fentanyl[28] and tramadol[29,30] as an adjuvant to local anesthetic have observed rapid onset of sensory and motor block similar to the present study. Duration of sensory and motor block was prolonged in the previous studies using pure opioid agonist as an adjuvant in different doses which also supports our observation. Duration of postoperative analgesia was also

increased with pure opioid agonist adjuvant similar to the present study.

In our study, the onset of motor block was much faster than the onset of sensory block which supports the 'core and mantle' concept of Winnie et al[31]. According to this concept, the sensory fibers are situated centrally, and motor fibers are placed peripherally in the brachial plexus. So, local anesthetics, when administered for brachial plexus block, are absorbed earlier by peripheral motor fibers than central sensory fibers causing the earlier onset of motor block.

In a previous study by Nazir et al[18] who used 10 mg of nalbuphine (equivalent to 30 mg pentazocine) with 30 ml of 0.375% bupivacaine in SCBP block observed mean duration of sensory and motor block of 373.17 and 313.92 min respectively, which is similar to our study. The mean duration of analgesia observed by them was 389.33 min which is also close to the present study, but the onset time for the sensory and motor block was faster in a previous study (4.89 and 8.83 min respectively). This may be due to a higher volume of local anesthetic used by the other study.

Another study using nalbuphine (10 mg) with 30 ml of 0.5% levobupivacaine in SCBP block has found a longer mean duration of sensory (519.11 min) and motor (484.54 min) block along with a longer duration of analgesia (531.45 min)[19]. This difference from our study may be due to the higher dose and volume of levobupivacaine used in their study compared to a lower dose of bupivacaine in the present study.

Study by Chiruvella et al[20] has also observed a longer duration of sensory block (708.67 min) and duration of analgesia (833.55 min) than the present study where they used 10 mg of nalbuphine with 29 ml of 0.375% levobupivacaine for brachial plexus block. The duration of the motor block (418.4 min) was close to our observation.

A study by Vengadessane et al[21] has observed a longer duration of block and postoperative analgesia with a lesser dose of the drug (nalbuphine 50 μg/kg with 20 ml of 0.5% bupivacaine). This may be attributable to the use of ultrasound in their study.

Study by Bharathi et al[22] has recorded mean sensory block (396.23 min), motor block (305.6 min) and duration of analgesia (511.73 min) with 1 mg nalbuphine (equipotent to 30 mg of pentazocine) in brachial plexus block which is similar to the present study.

Previous studies, where 2 mg of butorphanol was used with local anesthetic for SCBP block, have also recorded longer duration of block and analgesia[22,23].

In the present study, patients of pentazocine with bupivacaine group had a higher sedation score compared to patients who received only bupivacaine (Table 3). This sedation may be caused by the absorption of pentazocine by the blood vessels present in the tissue surrounding the brachial plexus. This absorbed pentazocine present in blood vessels crosses the blood-brain barrier and acts as an agonist on the kappa receptor which produces sedation[32]. This is similar to the study by Bhatia et al[23] with butorphanol with axillary brachial plexus block.

The present study is not without limitations. Ultrasound guidance for the brachial plexus block was not used as it was unavailable. There is a possibility that with the use of ultrasound a lesser amount of local anesthetic could have been used. Pediatric and geriatric patients have not been included and fixed dose and volume of drugs on every patient has been used. A dose-ranging study using various doses of pentazocine to find out the most suitable dose of pentazocine in SCBP block is required. Patient and surgeon satisfaction scores were also not assessed in the present study. We also did not evaluate the 24-hour rescue analgesic requirement.

Conclusion

From this study it can be concluded that the addition of pentazocine to bupivacaine in supraclavicular brachial plexus block resulted in a significantly early onset of sensory and motor block, prolonged duration of both sensory and motor block and prolonged duration of analgesia when compared with bupivacaine alone without any significant changes in hemodynamic and without any significant adverse effects.

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