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A Clinical Comparative Study of Butorphanol Versus Buprenorphine as an Adjunct to Local Anaesthetic Solution of Bupivacaine in Supra Clavicular Brachial Plexux Block

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ABSTRACT
Postoperative pain relief is mainly based on opioids. However the use of conventional administration of opioid through intramuscular, intravenous routes is associated with a variety of perioperative side effects like ventilatory depression, sedation, postoperative nausea and vomiting (PONV), pruritus, urinary incontinence, ileus, constipation Peripheral blockade remains a well accepted component of comprehensive anaesthetic care. The existence of opioid receptors in peripheral nerve tissue has led incorporating small doses of opioids in peripheral nerve blocks. The objective of this study is to compare between Butorphanol with local anaesthetics and Buprenorphine with local anaesthetics in supra clavicular brachial plexus block with respect to. Duration of sensory and motor blockade. Duration of analgesia. Untoward side effects. Secondary objective was to study any difference in the onset of sensory and motor blockade between the Butorphanol and Buprenorphine groups. This single-centre, double-blind, randomized controlled trial involved 100 patients scheduled for elective upper limb orthopaedic surgery. A comparative study consisting of 50 patients in Group A (Butorphanol) and 50 patients in Group B (Buprenorphine) was undertaken to study the change pattern of hemodynamic, pain score by NRS, duration of analgesia, duration of sensory, duration of motor blockade and side effects. All patients received supra clavicular brachial plexus block with 0.25% Bupivacaine. Pain was assessed using a numerical rating scale in the post-anaesthesia care unit. Chi-square test and Mann-Whitney U test was used for analysis. A P value <0.05 was considered to be statistically significant. There was no significant difference in the mean time of onset of sensory block between Group A and Group B (p=0.1998). There was no significant difference in the mean time of onset of motor block between Group A and Group B (p=0.1687). There was no significant difference in the mean duration of sensory block between Group A and Group B (p=0.7759). There was no significant difference in the mean duration of motor block between Group A and Group B (p=0.9505). However there was significant difference in the mean duration of analgesia between Group A and Group B (p<0.0001). The difference in the total number of analgesic doses consumed by Group A and Group B was also statistically significant with Group A consuming more number of analgesic doses. From this study it was observed that both buprenorphine and butorphanol prolonged the duration of analgesia. Buprenorphine (3 mcg/kg body weight) prolonged the duration of analgesia and decreased the need of rescue analgesic doses more than butorphanol (0.03 mg/kg body weight), when added as an adjunct to local anaesthetic solution into the brachial plexus sheath for peri-operative analgesia during upper limb surgery without any significant changes in the block characteristics or any complications observed in either group.

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Key Words
Anaesthesia, supra clavicular brachial plexus block, peripheral nerve simulator, postoperative analgesia, opioids, local anaesthetic solution

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INTRODUCTION

The alleviation of pain is the main concern of anesthesiologist. Uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects[1]. **Acute** effects include sodium and water retention and increased level of blood glucose, free fatty acids, ketone bodies and lactate, development of postoperative hypercoagulability giving rise to deep vein thrombosis[2], hyperglycemia contributing to poor wound healing and depression of immune function. Sympathetic activation may increase myocardial oxygen consumption, which may give rise to myocardial ischemia and infarction[2]. Decreased postoperative respiratory function are other effects of uncontrolled postoperative pain. **Chronic effects** include chronic post surgical pain which may interfere with patient's activities of daily living. Adequacy of postoperative pain control is one of the most important factors in determining when a patient can be safely discharged from a surgical facility and has a major influence on the patient's ability to resume their normal activities of daily living. Postoperative pain relief is mainly based on opioids. This may include conventional administration of opioid intramuscularly on demand as bolus or bolus intravenous administration, continuous intravenous infusion and patient controlled analgesia. Opioids can be administered by non parenteral routes as well, with predominantly buccal, sublingual, oral, rectal and transdermal ruling the market or by subarachanoid or epidural route, with or without local anaesthetic agents. Even though perioperative analgesia has traditionally been provided by opioids, the extensive use of opioids is associated with a variety of perioperative side effects like ventilatory depression, sedation, postoperative nausea and vomiting (PONV), pruritus, urinary incontinence, ileus, constipation that can delay hospital discharge. Pain relief after upper limb surgery can be achieved by various regional anaesthetic techniques. The supra clavicular brachial plexus block is one among the most popular regional nerve blocks performed. The existence of opioid receptors in peripheral nerve tissue has led to investigation of incorporating small doses of opioids in peripheral nerve blocks, hoping to achieve analgesia with minimal central side effects. The aim of this study is to compare the duration of postoperative analgesia between Butorphanol with local anaesthetics and Buprenorphine with local anaesthetics in supra clavicular brachial plexus block. The primary objective was to compare the duration of sensory and motor blockade, duration of analgesia, untoward side effects between the two groups. The secondary objective was to compare the onset of sensory and motor blockade between the two groups.

MATERIALS AND METHODS

After approval of the institutional ethical committee and after obtaining informed written consent from the patients, study was conducted in Silchar Medical College and Hospital, Silchar for 1 year on 100 patients undergoing upper limb orthopedic surgery under brachial plexus block. Patients with ASA1 and II physical status of age group of 20 years-60 years, of both sex were included in the study. Patients with coagulopathy or on anticoagulants, with peripheral neuropathy, with local cutaneous infections at the site of block, pregnant patients, patients with history of allergy to local anaesthetics, butorphanol and buprenorphine were excluded from the study. Randomization was computer generated using n Query software. Participants were randomised in a 1:1 ratio to receive supra clavicular brachial plexus block with 0.25% bupivacaine up to maximum dose of 2mg/kg body weight along with injection butorphanol 0.03mg/kg to the solution (Group A) or brachial plexus block with 0.25% bupivacaine up to maximum dose of 2mg/kg body weight with buprenorphine 3 mcg/kg into the solution (Group B). The total volume of local anesthetic given was 30ml-40 ml to both the groups. An anaesthetist prepared all study drugs and an independent anaesthesiologist performed PNB blocks in the block room. The patient, intraoperative anaesthesiologist and surgeon were blinded to group allocation. Blinded assessors recorded basic information. All the patients underwent thorough pre-anesthetic evaluation on the day prior to surgery. A written informed consent was taken. They were educated regarding the numerical rating scale. All the patients were fasted overnight. All of them received oral tablet Alprazolam 0.5mg and tablet Ranitidine 150mg night before the surgery. Patients were instructed about Numerical Rating Scale (NRS). Under aseptic conditions brachial plexus block was performed by supra clavicular approach using the peripheral nerve stimulation technique with the patients placed in supine position. A separate 5ml injection of 0.25% bupivacaine was made for an inter costo brachial nerve block in the axilla to provide anaesthesia for application of tourniquet. The **time of onset** for sensory blockade, defined as time between injection and total abolition of pinprick response, was evaluated in four nerve areas (radial, ulnar, median and musc cutaneous) at every 3 minutes until 45 minutes after the injection. The block was judged to be failed if anaesthesia was not present in 2 or more peripheral nerve distribution and such patients were excluded from the study. For motor block, the inability to flex or extend the following joints: musculocutaneous nerve (flex elbow), median nerve (flex distal interphalangeal joint of 2nd finger), radial nerve (extend wrist), ulnar

nerve (abduct 3rd and 4th fingers) was tested. **Time of onset of motor block**, defined as the time between injection of local anesthetic and inability to move the joints was evaluated every 3 minutes and time to block at least two major nerves was noted. The **duration of sensory blockade**, defined as the time between onset of action and return of pinprick response, was assessed every 30 minutes in at least 3 major nerve territory. The **duration of motor blockade**, was assessed every 30 minutes till the return of complete muscle power in at least 2 major nerve distributions. The **duration of analgesia**, defined as the time between the onset of action and the onset of pain, was the time when the patients received the first dose of analgesic. Supplemental analgesia was given in the form of intramuscular inj Diclofenac sodium 50-75 mg, when NRS score was >4. During surgery each group received standard ASA monitoring. Respiratory rate of less than 10 breaths per minute was considered as respiratory depression. No sedatives were given during surgery and degree of sedation was assessed immediately after giving the block which was considered as 0 hours and then 1 hourly for the first 6 hours followed by 2 hourly till 24 hours. The duration of surgery for both the groups was noted. Patients were evaluated post operatively, every hourly for first six hours, second hourly till twenty-four hours, for the following parameters-pulse, blood pressure, respiratory rate. Pain was assessed by standardized NRS score every hourly till 24 hours. Time to first dose of rescue analgesic required was noted. Patients were also monitored for the side effects like bardycardia, nausea, vomiting, drowsiness, pruritus, respiratory depression.

- Bardycardia is defined as a heart rate of below 60 beats/min.(dixit *et al*).
- Vomiting was defined as forceful expulsion of gastric contents from the mouth.
- Nausea was defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit. The data compiled were analyzed with Graphpad Instat® 3 statistical software. For qualitative data, Chi-square test was used. Quantitative data were analyzed using student t-test. For non parametric data Mann-witney test was used

RESULTS AND DISCUSSIONS

There was no significant difference in age, weight, sex distribution. Most of the patients had a time of onset of sensory block between 13-16 minutes in both the groups. The mean time of onset of sensory block in Group A was **14.12±3.06** min while in group B it was **13.3±2.99** min. The difference in the mean time of onset between Group A and Group B was not statistically significant **(0.1998).** The mean time of onset of motor block in Group A was 18.88±2.97min while in group B it was 18.06±2.94 min. The difference in the mean time of onset between Group A and Group B was not statistically significant **(p=0.1687)**. The difference in the mean duration of surgery between Group A and Group B was not statistically significant. The difference in the mean duration of sensory block and motor block between Group A and Group B was not statistically significant. The mean duration of sensory block in Group A was 397.8±52 min while in group B it was 400.8±53.1 minutes. The difference in the mean duration of sensory block between Group A and Group B was not statistically significant **(P=0.7759)**. The mean duration of motor block in Group A was 347.4±48.14min while in group B it was 346.8±48.17 minutes. The difference in the mean duration of motor block between Group A and Group B was not statistically significant **(P=0.9505).** Most of the patients in group A had a duration of analgesia between 8-11 hours. There were no patients in group A who had a duration of analgesia between 16-19 hours or 20-23 hours as the maximum duration of analgesia in group A was 14 hours. Most of the patients in group B had a duration of analgesia between 16-19 hours. No patient in group B had a duration of analgesia between 8-11 hours as the minimum duration of analgesia in group B was 15 hours. The mean duration of analgesia in Group A was 10.36±1.75 hours while in group B it was 19±2.22 hours. The difference in the mean duration of analgesia between Group A and Group B was statistically significant with p value <0.0001.

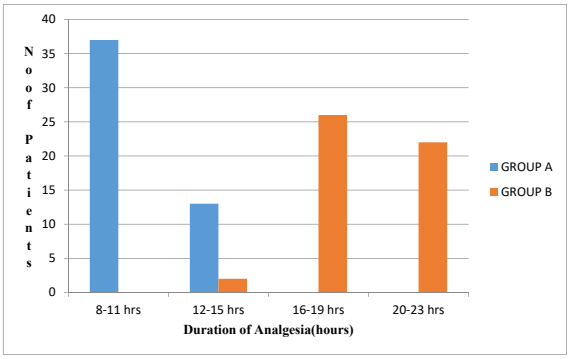

Fig. 1: Total Duration of Effective Analgesia

Total number of analgesic doses consumed by group A was 117 with a mean and standard deviation of 2.34±0.48 and total number of analgesic doses consumed by group B was 63 with a mean and standard deviation of 1.26±0.44.The difference was statistically significant (P<0.05). No complication or adverse events were observed in either of the groups.

To prolong perioperative analgesia various adjuncts such as opioids, clonidine, verapamil, neostigmine and tramadol have been tried[3]. There are various proposed mechanisms of the peripheral action of opioids. In injured tissue counteraction of pain occurs by interaction between leukocyte-derived opioid peptides and peripheral nociceptor terminals carrying opioid receptors[4] and by the action of anti -inflammatory cytokines[5]. There is an upregulation of opioid receptors in dorsal root ganglia, an increased axonal transport of opioid receptors and an accumulation of opioid receptors in peripheral nerve terminals during inflammation[6]. Opioids could also migrate to the posterior horn of the spinal cord after linkage with axonal receptors[6]. Inflammatory conditions entail a disruption of the perineurial barrier and this disruption clearly enhances the passage of opioid peptides to sensory neurons[7]. We chose to evaluate butophanol and buprenorphine as both these drugs are agonist-antagonist opioid analgesic. Butorphanol is a totally synthetic morphinan, considered to be a mixed agonist-antagonist opioid analgesic that has affinity for μ-, d-and k-opioid receptor subtypes[8]. Buprenorphine is highly lipid soluble, long acting with mixed agonist and antagonist effects. It binds to mu, kappa and delta opioid receptor subtypes and has a slow dissociation from these receptors. It is a centrally acting partial mu agonist and a kappa and delta antagonist[9]. Butorphanol is 10 times more potent than morphine, whereas buprenorphine has got an antinociceptive potency of 20-70 times higher than morphine. There are extensive studies on the use of both butorphanol and buprenorphine as adjuncts to local anesthetics in nerve blocks which shows better analgesia when these drugs are used in nerve blocks than their systemic use.

The Demographic Data of Patients in Our Study were as Follows:

Demographic Parameters Mean±SD	Group A(n=50)	Group B(n=50)	P value
Age in years	36.72±11.65	37.64±12.11	0.6995
Weight in kg	53.86±8.68	54.64±7.82	0.6379
Sex	Male=32(64%) Female=18(36%)	Male=29(58%) Female=21(42%)	0.6820
ASA status (I/II)	43/7	45/5	0.7596
Duration of surgery(min)	82.44±16.62	84.8±16.73	P=0.4808

Both the groups were comparable with respect to age, weight, sex and ASA status with no statistically significant differences. The duration of surgery was comparable in both groups with no statistically significant differences. In our study, premedication and anaesthetic techniques were kept constant to exclude any variation in responses due to a variety of drugs and technique. In our study most of the patients in both the groups had a time of onset of sensory block between 13-16 minutes. The mean time of onset of sensory block in Group A was 14.12±3.06 min while in group B it was 13.3±2.99 min with a p value 0.1998. The mean time of onset of motor block in Group A was 18.88±2.97 min while in group B it was 18.06±2.94 min. The difference in the mean time of onset between Group A and Group B was not statistically significant i.e , p>0.05. Most of the patients had a time of onset between 15-20 minutes in both the groups. So there was no significant difference in the time of onset of both sensory and motor blockade between the two groups. This was similar to the study by **K. S. Sanghvi**[10] where they compared the onset, quality and duration of block of buprenorphine, added as adjunct to bupivacaine in axillary brachial plexus block with plain bupivacaine. They found that addition of Buprenorphine (3μg/kg) to Bupivacaine mixture in peripheral nerve block did not affect the onset time for motor as well as sensory block. **Jadon**[12] in their randomized double-blind study to evaluate the analgesic efficacy of buprenorphine when added as adjunct to 0.3% bupivacaine in perivascular brachial plexus block, found that the duration of sensory block was prolonged in the beprenorphine group. In their study the duration of sensory block they found was 680.6±86. 27 minutes, where as in our study we found the duration of sensory block in the buprenorphine group to be 400.8±53.1 minutes. However in their methods they have mentioned that the duration of sensory blockade was considered as the time interval between the local anesthetic injection and the onset of pain in the postoperative period. In our study this criteria we have considered for the duration of analgesia. **Renu Wakhlo**[11] in their prospective randomized double-blind study found no change in the duration of sensory blockade in the butorphanol group as compared to the control group. The different durations of sensory blockade found in the different studies can be explained by the different definitions used in the different studies for the duration of sensory blockade. The difference in the mean duration of motor block between Group A and Group B was not statistically significant. Similar to our study**, A. Jadon**[12] found in their study that there was no prolongation of the duration of motor blockade on addition of buprenorphine to bupivacaine in perivascular brachial plexus block. The duration of analgesia found in the buprenorphine group of our study is comparable to the study by **Candido**[13] where they found a significantly longer duration of analgesia in the study group, which received brachial plexus block with local anesthetic and buprenorphine 0.3mg. In our study, the number of supplemental Diclofenac sodium injections received by group B was significantly <that received by group A. There was no significant difference in the hemodynamic parameters in both the

groups during the intraoperative period. From our study we observed that Buprenorphine is a superior adjunct than butorphanol when administered with local anaesthetic solutions into brachial plexus sheath for providing peri-operative analgesia following upper limb surgeries. There are certain limitations in our study. First we could have used ultrasonography guided nerve block and reduced the total volume of local anesthetic given. But due to the absence of this facility in our institution we could not go for this technique. Next in our study we did not have a control group and the pH of the administered solutions was not studied which are the other important factors that influence block characteristics.

CONCLUSION

From this study it was observed that both buprenorphine and butorphanol prolonged the duration of analgesia. Buprenorphine (3 mcg/kg body weight) prolonged the duration of analgesia and decreased the need of rescue analgesic doses >butorphanol (0.03mg/kg body weight), when added as an adjunct to local anaesthetic solution into the brachial plexus sheath for peri-operative analgesia during upper limb surgery without any significant changes in the block characteristics or any complications observed in either group.

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