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ORIGINAL RESEARCH

Effect of Addition of Buprenorphine and Buprenorphine with Verapamil to Local Anaesthetic in Brachial Plexus Block

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Abstract
Aim: To study the effect of adding 150µg buprenorphine alone or with 2.5mg verapamil to 1% lignocaine with 5µg/ml adrenaline (1:200000) in to brachial plexus sheath via supraclavicular approach on blockade characteristics and duration of analgesia.
Material and methods: The present study was conducted in the Department of Anesthesiology, at a tertiary care hospital in Maharashtra during the period of November 2007 to August 2009. One hundred and five consenting patients undergoing elective orthopedic upper limb surgeries were included in the study. Patients were randomly divided into three groups of 35 each receiving, Group C: 30cc of 1% Lignocaine + Adrenaline 5mcg/ml (1:200000), Group B: 30cc of 1% Lignocaine + Adrenaline 5mcg / ml (1:200000) containing 150mcg of Buprenorphine and Group BV: 30cc of 1% Lignocaine + Adrenaline 5mcg / ml (1: 200000) containing 150mcg of Buprenorphine and 2.5mg of Verapamil.
Results: The difference between mean onset time for sensory block (4.14 ± 1.14min., 4.2±1.15min. & 3.97±1.07min. in group C, B and BV respectively) was statistically insignificant ($p>0.05$). The quality of sensory and motor block according to Hollmen scale was comparable in the three groups ($p>0.05$). The mean duration of analgesia was 200.57 ± 28.89min. in group C, 637.71 ± 55.09min. in group B and 648.00 ± 61.82min. in group BV. It was significantly longer in group B and group BV compared to group C ($p<0.001$).
Conclusion: Thus, from our study we can conclude that, though 150µg buprenorphine does not affect blockade characteristics produced by 1% lignocaine with 5 µg/ml adrenaline in supraclavicular brachial plexus block, it provides more than 3 times longer duration of analgesia. Addition of 2.5mg verapamil to this combination, potentiates the local anesthetic by prolonging the duration of sensory and motor block, but does not improve the analgesia provided by 150µg buprenorphine.
Key Words: supraclavicular brachial plexus block, buorenorphine, verapamil, duration of analgesia, quality of analgesia.

Introduction

Regional anesthesia for upper extremity surgery is close to ideal match for patients, anesthesiologists, and surgeons. Successful block of the branches relies on the fact that these

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

branches are enveloped in a tubular sheath of fascia and if one of the branches is identified by eliciting paresthesia and a reasonably large volume of specific concentration of anesthetic agent is injected, block of entire plexus may be predicted. The supraclavicular block of the brachial plexus introduced by Labat in 1928 has many advantages over other approaches to brachial plexus block. It has the reputation of providing most complete and reliable anesthesia for upper limb surgery due to anatomic compactness of plexus at the trunk level where it is performed[1].

To get the anesthetic - analgesic effect with post-operative pain relief, numerous adjuncts like opioids, calcium channel blockers, benzodiazepines, steroids, clonidine, neostigmine, etc. have been added to local anesthetics in brachial plexus block and their effect on quality of block and duration of analgesia studied[2-3]. The demonstration that opioid receptors exist in the peripheral nervous system offers the possibility of providing post-operative analgesia in the ambulatory surgical patient. In an attempt to improve postoperative analgesia, a variety of opioids have been administered concomitantly with local anesthetics into the brachial plexus sheath[4-6]. The result of these studies have been inconclusive, with some investigators reporting prolonged analgesia while others observed no benefit from the use of brachial plexus opioids[6].

Viel et al (1989)[7] showed that the addition of 3µg/kg buprenorphine to 40ml of 0.5% bupivacaine provided almost twice the duration of post-operative analgesia as the addition of 50µg/kg morphine. Scott S. Reuben et al[3] for the first time used verapamil in brachial plexus block along with morphine and reported prolongation of duration of anesthesia with verapamil added to lidocaine – adrenaline in brachial plexus block but observed no effect on duration of analgesia. R. K. Vaswani et al[8] found prolongation of duration of blockade and post-operative analgesia with addition of verapamil to lignocaine-adrenaline with no effect on analgesia produced by brachial plexus tramadol.

Thus, the present study was designed to study the effect of adding 150µg buprenorphine alone or with 2.5mg verapamil to 1% lignocaine with 5µg/ml adrenaline (1:200000) in to brachial plexus sheath via supraclavicular approach on blockade characteristics and duration of analgesia.

Material and methods

The present randomized, prospective, double blind, controlled clinical trial study was conducted in the Department of Anesthesiology, at a tertiary care hospital in Maharashtra during the period of November 2007 to August 2009. Permission for conduct of the study was obtained from the ethical committee of the same institution. Written informed consent was obtained from each patient included in the study.

Primary outcome variable

Total duration of analgesia

Secondary outcome variables

- Onset of motor blockade
- Onset of sensory blockade
- Duration of sensory blockade
- Duration of motor blockade
- Quality of intra-operative analgesia.
- Hemodynamic stability of patient.
- Any adverse effects / complications.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

Sample Size
The duration of analgesia was the primary variable on which sample size estimation was based. Assuming 90% statistical power and setting the level of significance at 5%, an adequate sample size of 35 patients per group was calculated.

Study Population
Patients posted for elective orthopedic upper limb surgeries who were admitted in the orthopedic ward in Tertiary Health Care Hospital in Maharashtra.
It was a randomized, prospective, double blind, controlled clinical trial. One hundred and five consenting patients undergoing elective orthopedic upper limb surgeries were included in the study.

Inclusion Criteria
- ASA grade I / II
- Patients of either sex.
- Age between 18 - 60yrs.
- Weight between 40 – 70kg.
- Undergoing upper limb surgery to be carried out under brachial plexus block.

Exclusion Criteria
- Patients not willing to undergo the block
- Uncooperative or over anxious patient
- ASA III and IV patients or patients undergoing emergency surgery or patients with difficult airway.
- Patients with age <18yr or >60yr
- Patients with weight <40kg or >70kg
- Patients sensitive to local anesthetic
- Patients with local infection
- Patients receiving anticoagulants, opioids, adrenoreceptor agonists or antagonist therapy, β blockers, or verapamil.

Preoperative preparation
All patients were visited and pre-anesthetic evaluation was done thoroughly on the day prior to surgery. The anesthetic procedure to be undertaken including development of paresthesia, risks involved, effect of drugs to be given with the advantages of post-operative pain relief was explained to the patients and an attempt was made to alleviate the anxiety of the patient. Thereafter, informed consent was obtained and local anesthetic sensitivity testing was done. Height and weight of all the patients were noted. Minimum investigations like Urine examination for albumin & sugar, Complete blood count, Blood urea, Blood sugar, Bleeding time, Clotting time, Blood grouping, Cross matching and special investigations like KFT, LFT, ECG, X - ray Chest were done wherever indicated. Pre-anesthetic preparation of patients included a period of overnight fasting. All patients received 10mg diazepam orally at night before surgery. Patients were educated regarding the use of Visual Analogue Scale.

Procedure
Pre-operative pulse rate, systolic and diastolic blood pressure, respiratory rate and percent saturation of hemoglobin (SpO_2) were noted in the pre-anesthetic preparation room. Pre-operative Visual Analogue Score was also noted. NBM status of the patient was confirmed. In the operation theatre, ECG, Pulse oximeter, Non-invasive blood pressure monitor were

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

attached to the patient. An IV line was secured in the opposite upper limb with 20-gauge cannula and 50mg ranitidine IV started in infusion before the procedure. Sedation was avoided to minimize interference during assessment in quality of block. Patients were randomly divided into three groups of 35 each receiving,

Group C: 30cc of 1% Lignocaine + Adrenaline 5mcg/ml (1:200000)
Group B: 30cc of 1% Lignocaine + Adrenaline 5mcg / ml (1:200000) containing 150mcg of Buprenorphine.
Group BV: 30cc of 1% Lignocaine + Adrenaline 5mcg / ml (1: 200000) containing 150mcg of Buprenorphine and 2.5mg of Verapamil
Supraclavicular brachial plexus block was then performed with a 50 mm, 24-gauge puncture needle with 45° short-bevel connected to plexufix (B. Bräun).

Monitoring
Vital parameters (like pulse rate, systolic blood pressure, respiratory rate and oxygen saturation) of the patients were monitored every 1min. for 5 min., then every 5min. for next 20 min., then every 15 min. intra-operatively and half hourly post-operatively. Quality of analgesia was assessed subjectively by Visual Analogue Scale (VAS) which is a10cm scale with 0cm = no pain and 10cm = worst pain. After block placement, the pain assessment was done every 1min up to 5min, then every 5min for next 20 min and then every half hourly intra-operatively and post-operatively till patient received supplementary (rescue) analgesic in the form of 75 mg diclofenac IM. Patients were given rescue analgesic when VAS was ≥ 4. Quality of analgesia was considered "good" when patient had no pain (VAS = 0); "tolerable" when patient had mild pain but did not need an analgesic medication (VAS < 4); and "unsatisfactory" when patients pain was such that they needed analgesic medication (VAS ≥ 4). Patients were observed at regular intervals for evidence of any complication related to technique and drugs used.

Statistical analysis
Parametric and non-parametric data were collected and were entered in master chart in Microsoft Excel worksheet 2007. Data were analyzed by SPSS (version 14) software. Quantitative data was expressed as mean ± SD. Patient characteristics, duration of surgery, onset, completion and duration of sensory and motor block, duration of analgesia between the three groups were compared statistically by one-way analysis of variance (ANOVA) test and post-hoc comparisons were done with Dunnett-t test and for comparing quality of sensory and motor block Chi-square test was used. Hemodynamic and respiratory parameters were compared from their pre-operative values at various time intervals using paired "t" test. Pain scores (VAS) were compared using Kruskal Wallis and Mann Whitney μ test. For all purposes, probability value was considered significant when p-value was less than 0.05 and was considered highly significant when p-value was less than 0.001.

Results
The patients in the age range of 18-60yrs. were included in the study. Around 71% patients were in the age range of 18-40yrs. Mean age of the patients were statistically comparable among three groups ($p>0.05$). In all groups, male outnumbered the females. Maximum number of surgeries performed on the patients included in the study were plating of forearm bones (37.14%). The three groups were well matched with respect to type of surgical procedures.
The difference between mean onset time for sensory block (4.14±1.14min., 4.2±1.15min. & 3.97±1.07min. in group C, B and BV respectively) was statistically insignificant ($p>0.05$) as shown in table 1.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

Onset of sensory block in min.		No. of patients	
	Group C (n=35)	Group B (n=35)	Group BV (n=35)
< 1	0	0	0
1-2	2	2	3
3-4	21	22	22
5-6	11	9	10
> 6	1	2	0
Mean ± SD	4.14 ± 1.14	4.2 ± 1.15	3.97 ± 1.07

Table 1: Distribution of patients according to onset of sensory block

Onset of motor block was achieved within 6min. in 88.57% patients in group C, 80% in group B and 82.75% patients in group BV. Only one patient belonging to group C showed motor onset after 8min. The mean time of onset of motor block were statistically comparable between the three groups (p>0.05) as shown in table 2.

Onset of motor block in min.		No. of patients	
	Group C (n=35)	Group B (n=35)	Group BV (n=35)
<1	0	0	0
1-2	0	0	0
3-4	3	2	12
5-6	28	26	17
7-8	3	7	6
>8	1	0	0
Mean ± SD	5.57 ± 1.09	5.77 ± 0.84	5.2 ± 1.30

Table 2: Distribution of patients according to onset of motor block

Hollmen scale was used to assess the quality of sensory and motor block. Maximum patients (80% in group C, 85.71% in group B and 88.57% in group BV) were observed to achieve grade 4 of Hollmen scale for sensory blockade (i.e. no perception of pinprick). Only 7, 5 and 4 patients in group C, B and BV respectively recognized pinprick as touch with blunt object (Hollmen grade 3). Similarly, majority of patients (30 patients in group C and 31 patients each in group B & BV) had complete loss of muscle function (Hollmen grade 4) at 30min. of drug injection. The quality of sensory and motor block according to Hollmen scale was comparable in the three groups (p>0.05) as shown in table 3.

Grade of Sensory Block		No. of patients	
	Group C (n=35)	Group B (n=35)	Group BV (n=35)
1	0	0	0
2	0	0	0
3	7 (20%)	5 (14.28%)	4 (11.42%)
4	28 (80%)	30 (85.71%)	31 (88.57%)
Grade of Motor Block			
1	0 (0%)	0 (0%)	0 (0%)
2	0 (0%)	0 (0%)	0 (0%)
3	5 (14.28%)	4 (11.42%)	4 (11.42%)
4	30 (85.71%)	31 (88.57%)	31(88.57%)

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

Table 3: Distribution of patients according to quality of Sensory and Motor block

Mean duration of sensory block in group BV (185.14 ± 19.90min.) was significantly longer ($p<0.05$) compared to group C (159.85 ± 16.24min.) and group B (161.14 ± 19.02min.). Group C and group B was comparable with respect to duration of sensory block as shown in table 4.

Total duration of sensory block in min.		**No. of patients**	
	Group C (n=35)	**Group B (n=35)**	**Group BV (n=35)**
≤ 90	0	0	0
91-120	1	1	1
121-150	15	15	2
151-180	19	17	16
181-210	0	2	16
> 210	0	0	0
Mean ± SD	159.85 ± 16.24	161.14 ± 19.02	185.14 ± 19.90

Table 4: Distribution of patients according to total duration of sensory block

The mean duration of motor block was significantly longer in group BV ($p<0.05$) than group C and group B. No significant difference was noted between group C and group B ($p>0.05$) as shown in table 5.

Total duration of motor block in min.		**No. of patients**	
	Group C (n=35)	**Group B (n=35)**	**Group BV (n=35)**
≤ 90	0	0	0
91-120	22	20	7
121-150	13	15	24
150-180	0	0	4
Mean ± SD	123.00 ±12.49	124.71 ±13.50	140.57 ±14.13

Table 5: Distribution of patients according to total duration of motor block

Mean VAS was comparable among 3 groups pre-operatively and till 90min. after block placement table 6.

Time interval in hrs.		**VAS**	
	Group C (n=35)	**Group B (n=35)**	**Group BV (n=35)**
Pre Operative	7.42 ± 2.75	7.37 ± 2.7	6.97 ± 2.15
0	7.42 ± 2.75	7.37 ± 2.7	6.97 ± 2.15
½	0 ± 0	0 ± 0	0 ± 0
1	0 ± 0	0 ± 0	0 ± 0
1½	0 ± 0	0 ± 0	0 ± 0
2	0.22 ± 0.64	0 ± 0	0 ± 0
4	7.0 ± 2.82 (n=17)	0 ± 0	0 ± 0

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

6	-	0 ± 0	0 ± 0
8	-	0.31 ± 1.20	0.14 ± 0.69
10	-	1.82 ± 1.56 (n=29)	2.03 ± 1.86 (n=33)
12	-	4.33 ± 2.08 (n=3)	5.54 ± 2.20 (n=11)

Table 6. Distribution of patients according to fluctuations in mean VAS at different time intervals

The mean duration of analgesia was 200.57 ± 28.89min. in group C, 637.71 ± 55.09min. in group B and 648.00 ± 61.82min. in group BV. It was significantly longer in group B and group BV compared to group C ($p<0.001$). The mean duration of analgesia was comparable between group B and group BV ($p>0.05$) as shown in table 7.

Total duration of analgesia in min.	**No. of patients**		
	Group C (n=35)	**Group B (n=35)**	**Group BV (n=35)**
≤ 120	0	0	0
121-240	33	0	0
241-360	2	0	0
361-480	0	1	1
481-600	0	9	9
601-720	0	24	23
> 720	0	1	2
Mean ± SD	200.57 ± 28.89	637.71 ± 55.09	648.00 ± 61.82

Table 7. Distribution of patients according to total duration of analgesia

Discussion

To extend the analgesia beyond the operating rooms, different additives are used with local anesthetics. Various local anesthetics like bupivacaine, lignocaine, mepivacaine, tetracaine, etc are being used to block the conduction across nerve fibers in the brachial plexus block. Even with long acting local anesthetic like bupivacaine when used alone, the post-operative analgesia produced is of short duration. So, to achieve a better quality of anesthesia and analgesia intraoperative as well as post-operative and to reduce the toxicity of local anesthetic, various adjuvants to local anesthetic like opioids, α_2 agonists, benzodiazepines, steroids, anticholinesterases, etc have been tried[2-4].

In our study, onset of sensory block was before the onset of motor block in most of the patients. Similarly, time to achieve complete sensory block was earlier than time to achieve complete motor block in all the patients. This can be explained by the concept put forward by **De Jong et al**[9], authors stated that "because of lower C_m (minimum anesthetic concentration) of pain fibers compared to motor fibers, during induction of a nerve block, small sensory fibers in the nerve mantle will be blocked before their companion motor fibers." This observation was similar to **R.K. Yadav et al**[10]**, Ishrat Hussain et al**[11]**. Nishikawa K. et al**[12] have shown that addition of fentanyl to lidocaine in brachial plexus block resulted in an improved success rate of sensory blockade but a delayed onset of analgesia due to decreased pH of the mixture. **R. K. Vaswani et al**[8] observed significantly faster achievement of complete sensory and motor block attributed to tramadol.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

In our study, no significant differences in the onset and completion of sensory and motor block were noted in three groups. Our trend of observations regarding onset of sensory and motor block was similar to **Ashok Jadon et al**[6] while regarding time to achieve complete sensory and motor block was similar to **Scott S. Reuben et al**[3] **& Ishrat Hussain et al**[11]**.**

The mean duration of sensory and motor block were significantly longer in group BV than group C and group B. **Scott S. Reuben et al**[3] noticed significant prolongation of sensory anesthesia produced by lidocaine with adrenaline on addition of verapamil in to brachial plexus sheath, but no effect on blockade characteristics with addition of morphine. **R.K. Vaswani et al**[8] found that duration of sensory and motor block was significantly longer with tramadol and / or verapamil when added to lignocaine with adrenaline in brachial plexus block. Calcium permeability is reduced by local anesthetics, and verapamil, a calcium channel blocker has been shown to potentiate the effects of other local anesthetics.

Mean VAS was comparable among 3 groups pre-operatively and till 90min. of block placement. VAS score was significantly higher in group C as compared to group B and group BV after 2 hrs of block, but the mean VAS was still comparable ($p>0.05$) between group B and group BV. **Z. Wajima et al**[13] showed that 3 hr after operation, VAS scores were significantly higher in mepivacaine group and butorphanol group than in mepivacaine - butorphanol group. **Scott S. Reuben et al**[3] showed significant lower consumption of analgesics in the post-operative period in the groups where 5mg morphine with or without 2.5mg verapamil was used along with 1.5% lignocaine and 5µg/ml epinephrine in brachial plexus block. **Kenneth D. Candido et al**[14] found better quality of analgesia when buprenorphine was added to mixture of 1% mepivacaine and 0.2% tetracaine compared to that produced by local anesthetic mixture, in the early as well as late post-operative period. Similar findings were reported by **Sebastien Robaux et al**[15] and **Olfa Kaabachi et al**[4]. In our study no significant difference in mean VAS scores was noted at all time intervals between buprenorphine and combination of buprenorphine & verapamil when added to 1% lignocaine with adrenaline. Thus, addition of 150µg buprenorphine to 1% lignocaine with 1 : 200000 adrenaline significantly improved the quality of analgesia with no further improvement by addition of 2.5mg verapamil. 12,50). High lipid solubility and slow dissociation of buprenorphine from its receptors might be the reason for improvement in quality and duration of analgesia observed in our study.

In this study, addition of 150µg buprenorphine to 1% lignocaine and adrenaline in supraclavicular brachial plexus block prolonged the duration of analgesia more than 3 times that of the local anesthetic alone, the observations were at par with **Viel et al**[7]**, Kenneth D. Candido et al**[14]**, Salins S. R. et al**[16] and **Ashok Jadon et al**[6]**.** Also, duration of analgesia offered by addition of 2.5mg verapamil and 150µg buprenorphine to 1% lignocaine with adrenaline showed no significant difference with that provided by addition of 150µg buprenorphine alone, the findings were similar to **Scott S. Reuben et al**[3] and **R. K. Vaswani et al** [8]**. Janson W. et al**[17] stated that opioids could produce two types of effects on neuronal excitability, the first one is a local anesthetic action on the nerve fiber with a diminution of sodium and potassium conductance and the second is due to linkage of the opioid with a receptor on the internal face of the membrane. Opioid could also migrate to the posterior horn of the spinal cord after linkage with axonal receptors. These findings expand the gate control theory of pain and suggest new approaches such as development of peripherally acting opioid analgesics without central side effects. The peripheral action of opioid is also supported by the study of **Wajima Z. et al** (13).

In our study, the hemodynamic and respiratory parameters were stable in all the three group patients, so it can be concluded that any of the drugs used in our study i.e. 1% lignocaine with adrenaline, buprenorphine or verapamil after placement in the brachial plexus block might not have achieved significant plasma concentration to produce cardiovascular and respiratory effects related to local anesthetics, opioids and calcium channel blockers.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

In this study, the incidences of side effects were very less. All the side effects were observed in the first 4 hours of block placement. The most common side effect in our study was nausea and vomiting and the incidence was comparable among the three groups. Nausea was observed in 2 patients in group C, one patient in group B and 2 patients in group BV. Vomiting was observed in 1 patient in group C and 2 patients each in group B and BV. Nausea and vomiting was treated with 4mg ondansetron IV. No other side effects related to opioids like drowsiness, pruritus, respiratory depression, etc. or related to calcium channel blockers like arrhythmias or any other complications associated with supraclavicular block technique like pneumothorax, recurrent laryngeal nerve palsy, phrenic nerve palsy, etc., were observed in our study.

Z. Wajima et al[13], Kenneth D. Candido et al[14], Herve Bouaziz et al[18], R. K. Vaswani et al[8] and **Ashok Jadon et al[6]** reported minor side effects like nausea, vomiting, pruritus with no incidence of respiratory depression. **Ashok Jadon et al[6]** reported Horner's syndrome in 5 patients with no significant difference between the groups.

Conclusion

Thus, from our study we can conclude that, though 150µg buprenorphine does not affect blockade characteristics produced by 1% lignocaine with 5 µg/ml adrenaline in supraclavicular brachial plexus block, it provides more than 3 times longer duration of analgesia without any untoward side effects. Also, when added to 1% lignocaine + 5 µg/ml adrenaline with 150µg buprenorphine, 2.5mg verapamil potentiates the local anesthetic by prolonging the duration of sensory and motor block, but does not improve the analgesia provided by 150µg buprenorphine.

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