COMPARISON OF BUPIVACAINE, ALKALINIZED BUPIVACAINE AND FENTANYL BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK USING NERVE STIMULATOR: A DOUBLE BLIND RANDOMISED CLINICAL STUDY

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Abstract

This study was designed to compare the effect of plain bupivacaine (0.25%), alkalinized bupivacaine and fentanyl-bupivacaine mixture in supraclavicular brachial plexus block. It was a prospective, randomised, double blind study. A total of 60 otherwise healthy patients with physical status ASA I and II were randomly allocated to 3 groups of 20 each to receive either plain bupivacaine 30ml, alkalinized bupivacaine 30 ml (sodium bicarbonate 8.4%, 0.1ml/10 ml of bupivacaine) and fentanyl-bupivacaine (75µg fentanyl) 30ml. The mean time of onset of block and time to achieve complete block was faster in the group that received alkalinized bupivacaine compared to the other two groups. Quality of block was better and duration of analgesia was longer in the fentanyl-bupivacaine group. No difference was noted regarding side-effects/complications. The study suggests that alkalinization of plain bupivacaine (0.25%) significantly improves the supraclavicular block characteristics i.e., onset of block and time to achieve complete block. The quality of block as assessed by VAS scale is better and duration of analgesia is prolonged in fentanyl-bupivacaine group.

Keywords: Brachial Plexus Block, Supraclavicular, Bupivacaine, Alkalanized Bupivacaine, Fentanyl.

Introduction

‘Regional anaesthesia’ is a term first used by Harvey Cushing in 1901 to describe pain relief by nerve blocks¹. Regional nerve blocks are based on the concept that pain is conveyed by nerve fibers, which are amenable to interruption anywhere along their pathway². Local anaesthetic are drugs that produce reversible conduction blockade of impulses along central
and peripheral nerve pathways after regional anaesthesia. With progressive increases in concentrations of local anaesthetics, the transmission of autonomic, somatic sensory and somatic motor impulses is interrupted, producing autonomic nervous system blockade, sensory anaesthesia and skeletal muscle paralysis in the area innervated by the affected nerve. Removal of the local anaesthetic is followed by spontaneous and complete return of nerve conduction, with no evidence of structural damage to nerve fibers as a result of the drug’s effects. Local anaesthetic administered in regional nerve blocks often have short duration of action. Various opioids like fentanyl, morphine, tramadol, sufentanyl and non-opioids like hyaluronidase, midazolam, sodium bicarbonate, dexmedetomidine, clonidine, neostigmine have been added to local anaesthetics to lower doses of each agent and modify the block in terms of quick onset, good quality, prolonged duration and post-operative analgesia while reducing the incidence of adverse effects. It has been seen that time to onset of sensory blockade is reduced and significantly increased duration of analgesia is observed with alkanized bupivacaine 0.25%. The addition of bicarbonate in order to adjust its pH produces not only a change in pH but also an increase in PCO₂. Carbon dioxide very likely diffuses into the axon, acting as a membrane permeant acid, facilitating the formation of local anaesthetic in an active cation form within the axon. Peripheral nerves possess opioid receptors, and this has tempted clinicians to add narcotics to local anaesthetics to prolong the analgesic effects of these solutions. Also the addition of opioids to local anaesthetics in the brachial plexus block has no significant adverse effect on the respiratory and haemodynamic parameters when used in prescribed doses and has a minimal incidence of nausea and vomiting or other side effects. Fentanyl is one of the narcotic drug used as adjuvant to local anaesthetic in supraclavicular block.

Methods:

60 healthy adults of either sex aged 20-50 years, belonging to ASA physical status I or II undergoing below midarm surgery were recruited for this study. Exclusion criteria were progressive neurological disorder, sever liver or kidney disease, History of hypersensitivity to any of the study medication, Patients having opposite side pneumothorax or collapsed lung, patients having bilateral upper limb surgery, coagulopathy and patients on opioid or chronic analgesic therapy. During the pre-operative visit, all patients were clinically assessed, evaluated and investigated. On arrival to the operation theatre, peripheral I/V line was established with 20 Gauge cannula. Standard anaesthesia monitoring
was instituted [electrocardiogram, blood pressure (systolic, diastolic, mean), pulse oximetry].
All patients received Midazolam 1 mg intravenously as premedication before performance of
block. Drug solutions were prepared by an anaesthetist not involved in the performance of
block, in the patient care, or in data collection. The patients were randomly allocated to one
of 3 groups of 20 patients each. The anaesthetic solution was prepared according to a random
number table by means of a computer generated randomization list by an anaesthetist not
otherwise involved in the study. The anaesthetists performing the block were blinded to the
treatment group. The patients were also blinded to group allocation and interventions. All
observations were carried out by a single investigator who was also blinded to the treatment
group.
Group I:- Patients were given 30ml solution of 0.25% bupivacaine for supraclavicular
brachial plexus block.
Group II:- Patients were given freshly prepared alkalinized 30 ml solution of 0.25%
bupivacaine for supraclavicular brachial plexus block. Alkalinization was performed by
adding sodium bicarbonate 8.4% (0.1ml per 10ml of bupivacaine).
Group III:- Patients were given 30ml solution of 0.25% bupivacaine with 75microgram(µg)
fentanyl for supraclavicular brachial plexus block.
Brachial plexus block was performed by supraclavicular approach with 22G short bevel, 4-
cm needle using nerve stimulator technique. The nerve stimulator that we used in our study
was Micro-controller based nerve stimulator (LCD-GEMI-Model: DSL-007). Needle was
supposed to be placed accurately when paresthesia were elicited (isolated muscle twitch of
the fingers) and after aspiration to exclude IV placement of the needle, local anaesthetic was
injected in incremental doses. Intraoperatively, heart rate, oxygen saturation and blood
pressure (Systolic, diastolic, mean arterial pressure) was measured every five minutes till
completion of surgery. If systolic B.P decreased to< 90 mmHg or decreased >30% of
baseline, ephedrine 5 mg was administered. If heart rate decreased to <50/min, atropine 0.6
mg iv was given.

**Results:**
The three groups were comparable with respect to age and did not show statistically
significant difference (p-value>0.05) with mean age of 29.3±4.89, 30.9±4.43 and 30.2±3.58
years in group I, group II and group III respectively.
In group I, there were 16 males and 4 females, in group II there were 15 males and 5 females,
whereas in group III there were 14 males and 6 females respectively. The difference in male/female ratio among the three groups were statistically insignificant (p>0.05).

Mean weight (kgs) in group I was 54.7±2.30, group II was 54.1±3.45 and group III was 55.2±4.32. There was no statistically significant difference between the three groups with respect to weight (p-value>0.05).

The mean duration of surgery in group I, group II and group III were 99.7±3.31, 103.1±5.78 and 101.3±4.87 minutes respectively. The comparison between the three groups was statistically insignificant (p>0.05) with respect to duration of surgery.

The mean heart rate at different time intervals did not differ significantly between the three groups.(p-value>0.05).

The mean arterial blood pressure (mmHg) between the three groups was not statistically different at different time intervals.(p-value>0.05).

Mean oxygen saturation did not differ significantly between the three groups at different time intervals.(p-value>0.05).

Mean time to onset of block was 14.6±1.54 mins in group I, 7.6±1.32 mins in group II, and 11.4±1.50 mins group III. It can be inferred that onset of block was significantly faster in group that received Alkalinized bupivacaine (group II) compared to both group I (Bupivacaine) and group III (Fentanyl –bupivacaine) (p-value <0.05). Also when comparing the mean time to onset of block in group I (Bupivacaine) and group III (Fentanyl bupivacaine) it was found that onset of block was significantly rapid in group III (p-value<0.05) compared to group I.

Complete block in our study was defined as all segments having analgesia and anaesthesia. The mean time to achieve complete block in group I, group II and group III were 26.3±1.94, 17.0±1.23 and 21.0±2.05 mins respectively. There was a statistically significant difference in the groups with respect to time to achieve complete block with fastest time being noted in group II (Alkalinized bupivacaine) compared to both group I (Bupivacaine) and group III (Fentanyl-bupivacaine).
Mean VAS score at 30 min in group I, group II and group III were 2.70±0.47, 2.35±0.49 and 2.15±0.37 respectively. The mean VAS score at 30 min was lowest in group III and the difference was statistically significant (p-value=0.001) compared to both groups I and group II. We observed a significant difference in VAS between group I and II. However, there was no significant difference in VAS scores between group II and III (p-value=0.161).

At 1 hour, mean VAS score in group I, group II and group III was 2.70±0.47, 2.65±0.09 and 2.20±0.41 respectively. There was a statistically significant difference in VAS score between group II and III & group I and group III at 1 hr with scores being lowest in group III. The difference between group I and II was not significant statistically.

Mean VAS scores at 2 hours in three groups were 2.85±0.37, 2.80±0.41 and 2.40±0.50 in group I,II and III respectively. The difference was significant between groups I and III &II and III, however it was insignificant between groups I and II.

Lowest VAS scores at 4 hours were observed in group III of 3.00±VVAS score was significantly different between groups II and III &I and III. When compared to group II, there was no significant difference in VAS score in group I.

A significant difference existed in VAS scores between group I and III,II and III with lowest score in group III of 3.30±0.47. The difference in VAS score between group I and II was statistically insignificant.

The Mean VAS score of 6 hours in the three groups was 3.12±0.29, 2.96±0.34 and 2.61±0.23 in group I, II and group III respectively. There was a significant variation between the three groups with respect to mean VAS score (p-value<0.05). Patients in group I were first to report pain in the postoperative period followed by group II. In group III, patients had adequate analgesia for a significant longer duration as compared to group I and group II.
The duration of analgesia was maximum with the addition of fentanyl (464.8±38.98 mins) as compared to bupivacaine (238.5±12.12 mins) and alkalinized bupivacaine (316.0±11.88mins) and the difference was statistically significant among all the three groups(p<0.001).

The difference in number of rescue analgesia doses required among three groups were comparable and did not show any statistically significant difference (p>0.05).

The sedation score among three groups were comparable and did not show any statistically significant difference (p>0.05).

With respect to complication profile among the patients, the commonest was nausea and pruritus 5% (n=1) in group III respectively. None of the patients in either of the groups developed pneumothorax or bradycardia. When all the groups were compared with one another, the difference between the groups was found to be statistically insignificant. (p-value>0.05).

**Discussion**

Peripheral nerve blocks are cost effective anaesthetic techniques used to provide anaesthesia and analgesia while avoiding airway instrumentation and hemodynamic consequences of general anaesthesia. Patient satisfaction, a growing demand for cost effective anaesthesia and a favourable postoperative recovery profile have resulted in increased demand for regional techniques. Brachial plexus block is an easy and relatively safe procedure for upper limb surgeries. Various approaches like supraclavicular, interscalene, infraclavicular and axillary have been used for blocking the brachial plexus. Supraclavicular approach to brachial plexus block is associated with rapid onset and reliable anesthesia. Various local anaesthetic agents (bupivacaine, levobupivacaine, mepivacaine, ropivacaine) are used for brachial plexus block with good results obtained. However, since the demonstration of opioid receptors in the peripheral nervous system, the use of opioids alone or in combination with local anaesthetics for peripheral nerve block has aroused
interest. It has been suggested that peripheral administration of opioids improves the analgesia and reduces systemic side effects and total dose of local anaesthetics required. Alkalization of local anaesthetics has been demonstrated to reduce the time to onset, improve the quality of analgesia and prolong the duration of anaesthesia.

All the three groups were homogenous with reference to age, sex, body weight and duration of surgery. Heart rate, mean arterial blood pressure and oxygen saturation by pulse oximetry was recorded at various intervals in perioperative period but the difference between the groups was statistically insignificant.

The mean onset of action of block was 14.6±1.54 minutes in group I, 7.6±1.32 minutes in group II and 11.4±1.50 minutes in group III (Table 11). Onset of action was decreased in group II. Order of onset of block was group II>III>I. This rapid onset of blockade in group II is attributed to the addition of sodium bicarbonate 8.4% in our study subjects. It is well known that relative alkalinity of local anaesthetic may be a major determining factor in altering the onset of action of local anaesthetic. Increasing the pH towards pKa of a drug by alkalisation increases the concentration of non ionized form and it is this non ionized fraction that diffuses rapidly to the inner axonal surface producing quicker onset of analgesia. Our results are in congruence with Hilgier et al and Mc Morland et al who performed a double blind study to evaluate the effect of alkalinized bupivacaine and bupivacaine with epinephrine 1:200000 (pH-3.9). They observed the rapid onset of sensory analgesia in patients who received alkalinized bupivacaine.

The difference in time to achieve complete block was statistically significant with mean of 26.3±1.94 minutes in group I, 17.0±1.23 minutes in group II and 21.0±2.05 minutes in group III (Table-12). Order of block was group II>III>I. Addition of sodium bicarbonate to bupivacaine significantly shortened the time required to achieve complete block. Our study is in congruence with Singh S.P et al (2009) who in their study showed that alkalinisation of bupivacaine not only increases the pH of the solution but also PC02. Carbon dioxide very likely diffuses into the axon, acting as membrane permeant acid, facilitating the local anaesthetic in an active cationic form within the axon which affects the block characteristics i.e, decreases the time to achieve complete block.

On comparing the Visual Analogue Scale (VAS) score between the three groups at various intervals i.e; 30 minutes, 1 hr, 2 hr, 4 hr, 6 hr, a statistically significant difference was found (p<0.001) (Table-13,14,15,16,17 &18). A mean VAS score of 3.12±0.29 was found in group I, 2.96±0.34 in group II and 2.61±0.23 in group III. The VAS score in group III was lower.
than group II and group I. Patients in group III had a longer period of subjective comfort as compared to group II and group I.

Our observation are in congruence with those of Parikh R.K et al (1995)\textsuperscript{12}. They observed that addition of fentanyl 0.2\(\mu\)g/ml to the solution increased the degree of analgesia. This has been attributed to the antinociceptive effects of fentanyl due to activation of opiate (\(\mu\)) receptors present peripherally on primary afferent nerves. Secondly, fentanyl may also provide analgesia through central opioid receptor-mediated analgesia by peripheral uptake of fentanyl to systemic circulation.

Kardash K et al\textsuperscript{13} observed a significant decrease in VAS score in the patients who received fentanyl and bupivacaine in brachial plexus block at 1 hour after surgery. This is consistent with our results.

There was a statistically significant difference as regards the duration of analgesia with a mean of 238.5\(\pm\)12.12 minutes in group I, 316.0\(\pm\)11.88 minutes in group II and 464.8\(\pm\)38.98 minutes in group III (Table-19). In our study the duration of analgesia was more prolonged in patients who received fentanyl with bupivacaine as compared to patients who received plain bupivacaine or alkalinized bupivacaine. Our study is in concordance with Parikh R. K et al (1995)\textsuperscript{12} who reported prolonged duration of analgesia with fentanyl in supraclavicular block.

It was seen in our study that the mean number of rescue analgesia doses in group I, group II and group III were 1.6\(\pm\)0.51, 1.4\(\pm\)0.50, 1.3\(\pm\)0.47 respectively . The difference between the groups was found to be statistically insignificant (\(p=0.075\)). However, due to prolonged duration of analgesia observed with fentanyl, number of rescue analgesia doses required were lower in the group that received fentanyl+bupivacaine (group-III) when compared to plain bupivacaine (group-I) and alkalinized bupivacaine (group-II). However, it was statistically insignificant (\(p\)-value<0.05). Our study is in congruence with Singh S.P et al(2009)\textsuperscript{10} who reported no difference of number of rescue analgesia doses among any of the study groups.

There was a statistically insignificant difference as regards to sedation score (postoperatively for 6 hours) with a mean of 0.85\(\pm\)0.37 in group I, 0.80\(\pm\)0.41 in group II and 0.90\(\pm\)0.45 in group III. Post-operative sedation in the group III (fentanyl+bupivacaine) was attributed to peripheral uptake of fentanyl into systemic circulation and its subsequent action in the central nervous system. Our study is in congruence with Singh S.P et al (2009)\textsuperscript{10} who reported no statistically significant difference in the incidence of postoperative sedation among any of the study groups.
All the studied patients were followed for 24 hrs in post operative period and were especially monitored for the development of nausea, vomiting, pruritus, bradycardia, pneumothorax, nerve injury. Only one patient in our study subjects in group III(fentanyl-bupivacaine) developed nausea and one patient developed pruritus (Table-22). The difference among the three groups was statistically insignificant (p>0.05).

Carlo D Franco\textsuperscript{14} demonstrated decreased incidence of direct nerve injury or intra-neural injection of local anaesthetic when using peripheral nerve stimulator technique. Their results are in congruence with ours as we have used nerve stimulator in our study.

A limitation of our study was that a larger sample size could have added more precision to our results. Secondly, the incorporation of an ultrasound guided block localization technique could have drastically decreased the total volume of local anaesthetic which was administered and this could have added new dimensions to our study.

**Conclusions:**

Supraclavicular block is a safe, reliable and cost effective technique of providing anaesthesia for upper limb surgery (below mid-arm surgeries).

Alkalization of 0.25% Bupivacaine significantly improves the supraclavicular block characteristic that is, shortens time of onset of block, decreases time to achieve complete block without any unwanted increase in side effects.

Addition of Fentanyl also shortens the time of onset of block, decreases the time to achieve complete block but not to the same extent as with alkalization of Bupivacaine, however quality of block is better and duration of postoperative analgesia is greater with the addition of Fentanyl to Bupivacaine.

**Bibliography:**