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COMPARATIVE EVALUATION OF EFFICACY AND DURATION OF ANALGESIA OF CLONIDINE AND DEXMEDETOMIDINE AS ADJUVANT TO BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS NERVE BLOCK IN UPPER LIMB ORTHOPAEDIC SURGERY

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ABSTRACT

Background:*Supraclavicular brachial plexus block using local anaesthetics along with various adjuvants is widely employed for perioperative anaesthesia and analgesia in surgeries of upper extremities. We compared efficacy of alpha-2 agonists namely clonidine and dexmedetomidine as adjuvants to bupivacaine in supraclavicular block for upper limb orthopedic surgeries with respect to onset of sensory and motor block, duration of sensory block along with haemodynamic variables, sedation score and side effects profile.*

Method:*Eighty ASA I and II patients scheduled for elective upper limb orthopedic surgeries under supraclavicular brachial plexus block were divided into two equal groups in a randomized, double-blinded fashion. Group C received clonidine 1 μg/kg and Group D received dexmedetomidine 1 μg/kg added to bupivacaine 0.25% (38 ml). Onset time of sensory and motor block, duration of analgesia, quality of block, cardiorespiratory variables, sedation scores, side effects were studied in two groups.*

Result: *The time of onset of sensory block in Group D (6.85 ± 2.27 minutes) was significantly higher than in Group C (10.17 ± 1.65 minutes). Onset time of motor block in Group D (9.10 ± 2.83 minutes) was significantly higher than in Group C (12.52 ± 1.37 minutes). Time to rescue analgesic was significantly higher in Group D (894.75 ± 63.30 minutes) than in Group C (606.75 ± 22.17 minutes). Nine patients in Group D and two in Group C developed bradycardia whereas five patients in Group D and two in Group C developed hypotension.*

Conclusion: *Dexmedetomidine (1µg/kg) when added as adjuvant to bupivacaine (0.25%) in supraclavicular brachial plexus block, enhanced the onset of sensory and motor block when compared with clonidine (1 µg/kg). Time for rescue analgesic requirement was prolonged in patients receiving dexmedetomidine in comparison to clonidine. Perineural dexmedetomidine produces hypotension, bradycardia more than clonidine but these can be reversed easily.*

Keywords: Analgesia, Clonidine, Dexmedetomidine, Bupivacaine, Supraclavicular nerve block

Introduction

Upper limb surgeries are mostly performed under peripheral nerve blocks such as the brachial plexus nerve block and it is a good alternative to general anaesthesia. Peripheral nerve blocks not only provide intraoperative anaesthesia but also provide analgesia in the post-operative period without any systemic side effects.[1] The classical approach using paresthesia technique being a blind technique may be associated with higher failure rate and injury to the nerves and vascular structures.[2] To avoid some of these problems use of peripheral nerve stimulator was started which allowed better localization of the nerves/plexus.[3,4] The current study was designed to test the hypothesis that dexmedetomidine when added as an adjuvant to local anaesthetic in supraclavicular brachial plexus block enhanced the duration of sensory and motor block and duration of analgesia as compared with clonidine.

Aims and Objectives

The aim of the present study was to compare the efficacy and duration of analgesia of clonidine and dexmedetomidine as adjuvant to bupivacaine in supraclavicular brachial plexus nerve block in upper limb orthopedic surgery.

Specific objectives of this study are

1. To compare the onset of sensory block between two groups.
2. To compare the onset of motor block between two groups.
3. To compare the duration of analgesia between two groups.

4. To find out the cardio-respiratory variables between two groups.
5. To compare degree of sedation between two groups.
6. To see any adverse effects.

Materials and Methods

Sample size

Sample size was calculated from previous study and using following formula given below:

$$N = \frac{2 \times S^2 \times (Z_\alpha + Z_\beta)^2}{D^2}$$

[N = Sample size equal in each group
SD = Standard deviation
Zα = Z value for alpha error (at 95% confidence level, it is 1.96 in two tailed)
Zβ = Z value for beta error (20% beta error and 80% power, it is 0.84 in one tailed)
D = mean difference to be detected]

Calculated Sample Size in our study was 40 (N = 40) in each group

Parameters to be studied:

1. Onset of sensory block was the completion of injection of study drug to loss of pin prick sensation, as assessed, using a 3 point scale for pain (Gormley and Hill) by pin-prick with 23G needle (0=normal sensation, 1= loss of sensation to pin prick (Analgesia), 2= loss of sensation to touch (Anaesthesia).[5]

2. Onset of motor block was the completion of injection of study drug to first loss of motor power which was assessed by modified Lovett rating scale.[6] (6.- Normal muscular force, 5. Slightly reduced muscular force, 4. Pronounced reduction of muscular force, 3. Slightly impaired mobility, 2. Pronounced mobility impairment, 1. Almost complete paralysis, 0. Complete paralysis)

3. Intensity of pain was assessed by 0-10 linear Visual Analogue Scale (VAS) on which 0 indicated no pain and 10 indicated the worst pain imaginable.[5]

4. Duration of analgesia was the end point when patient required rescue analgesic.

5. The degree of sedation was assessed using Modified Ramsay Sedation Scale.[7]

6. Cardio-respiratory variables [i.e. SpO_2, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Heart Rate (HR), ECG] were assessed by Pulse oximeter, NIBP and ECG monitoring.

Study tools:

- 3-point scale for pain (Gormley and Hill)
- Modified Lovett rating scale
- VAS (Visual Analogue Scale)
- Modified Ramsay Sedation Scale
- Multichannel monitor (Philips IntelliVue MP30)
- Nerve locator Plexygon, 7501.31; Vygon, Italia S.r.l., Italy.
- Weighing machine and measuring tape, stethoscope, torch.
- I.V. cannula, infusion set, lactated ringers' solution, disposable syringes
- Patient's bed head ticket, previous investigation reports.

After obtaining Institutional Ethics Committee Clearance and informed written consent from all patients, our prospective randomized double blind study was carried out in the Department of Anaesthesiology of Bankura Sammilani Medical College and Hospital, Bankura. Eighty patients, aged between 18-60 years, of either sex with American Society of Anaesthesiologists Physical status I and II (ASA-PS I and II) undergoing elective upper limb orthopedic surgery were enrolled in our study. Patient's refusal, patients having known allergies to any of the drugs, infection at the site of block, patients with any co-morbid condition like neurological, neuromuscular, cardiovascular, pulmonary, renal and hepatic diseases, patients with psychiatric disorder, h/o convulsion, coagulopathies or any bleeding disorder, patients on anticoagulants, pregnant and lactating mothers, operation on shoulder joint, patients with phrenic nerve palsy**,** pneumothorax**,** failed block were excluded from the study.

All patients were randomly divided into two groups with the help of lottery method into Group C (clonidine group) and Group D (dexmedetomidine group) and each group had 40 patients (n=40). Group C (n=40) patients received 38 ml 0.25% bupivacaine plus clonidine (1µg/kg body weight) and Group D (n=40) patients received 38 ml 0.25% bupivacaine plus dexmedetomidine (1µg/kg body weight). Calculated dose of dexmedetomidine or clonidine according to patients' body weight was taken in another 2 ml syringe and diluted by sterile

water to make 2ml. So, total 40 ml volume was injected in both groups. The anaesthetic solution was prepared by an anaesthetist not otherwise involved in this study. The anaesthetist performing the block and observing the effects were also blinded to treatment group.

On the day before surgery, all patients were examined properly. Routine blood investigations, chest X-Ray, ECG were done in all patients. All patients included in our study were premedicated with tablet alprazolam 0.25mg and tablet omeprazole 20 mg at bedtime the night before surgery. They were fasted from 10 pm onwards on the previous night. Patients were also counseled and demonstrated about visual analogue scale and how to express the pain intensity at the pre-anaesthetic visit on the day before surgery. In the operating room, patients were connected to the non invasive multichannel monitor (Philips IntelliVue MP30) and baseline parameters such as heart rate (HR), from ECG, Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Saturation of oxygen (SpO_2) were obtained and continuous monitoring was done thereafter. Anaesthesia machine, all equipments and drugs for emergency resuscitation were kept ready. Intravenous line was established with 18G cannula and infusion with Ringer Lactate was started. All the patients were explained about the procedure first. The patients were placed in a supine position with the head turned away from the side to be blocked. The upper limb to be anaesthetized was adducted and extended along the side towards the ipsilateral knee as far as possible. Antiseptic dressing and draping of the site was done. Nerve stimulator (Plexygon, 7501.31; Vygon, Italia S.r.l., Italy) was switched on and one wire connected to disposable silver chloride electrode and the other wire was connected to needle (22 G, 5 cm insulated needle). Using classic technique approach of supraclavicular brachial plexus nerve block, and using the Nerve stimulator (Plexygon, 7501.31; Vygon, Italia S.r.l., Italy) to locate the brachial plexus, 40 ml. of the anaesthetic solution was administered slowly performing negative aspiration in every 5-6 ml to avoid intravascular injection. Assessment of sensory block by response to pinprick using 3 point scale for pain (Gormley and Hill), was carried out at every 2 minutes after completion of drug injection in the dermatomal areas, corresponding to median nerve (thenar eminence), radial nerve (first web space), ulnar nerve (hypothenar eminence) till complete sensory blockade. Sensory onset was considered when there was loss of sensation to pin prick (analgesia) along the distribution of any of the above-mentioned nerves. Complete sensory block was considered when there was loss of sensation to touch (anaesthesia). Assessment of motor block by modified Lovett rating scale ranging from 6 (usual muscular force) to 0 (complete

paralysis), was carried out at every 2 minutes, till complete motor blockade after drug injection. Motor block was evaluated by thumb abduction (radial nerve), thumb adduction (ulnar nerve), thumb opposition (median nerve), and flexion at the elbow (musculocutaneous nerve). Onset time of motor block was defined as, the time interval of completion of injection of study drug to first loss of motor power. Peak motor block was considered when there was Grade 0 motor blockade. In peroperative period, haemodynamic variables (HR, SBP, DBP & MAP), SpO_2 and Sedation score were measured at 0, 5, 10, 15, 30 and 45 minutes and also in postoperative period, haemodynamic variables (HR, SBP, DBP & MAP), SpO_2 and Sedation Scores were measured at 0, 2, 6, 12 and 24 hours. Both peroperative and postoperative sedation score were measured by modified Ramsay sedation scale. Each patient was observed for complications like bradycardia, hypotension, dizziness, dryness of mouth, respiratory depression. Patients were discharged from post anaesthesia care unit (PACU) with stable vital signs. The postoperative intensity of analgesia was evaluated by using visual analogue scale (ranging from 0 to10) and rescue analgesic was given when VAS score was ≥ 3 and the time was noted. Duration of analgesia was determined by the end point when patient required first rescue analgesic (inj. diclofenac sodium 3mg/kg intramuscularly).

Statistical Analysis

Collected data were plotted in Microsoft office excel sheet and graphically represented and explained through various charts and tables. Data were analyzed by SPSS version 20 (statistical package for Social Sciences) software. Unpaired t-test was applied for quantitative data analysis and Chi-square test used for qualitative data analysis. P value was considered significant if <0.05 and highly significant if <0.001.

Results and Analysis

A total of 80 patients who underwent elective upper limb orthopedic surgeries were enrolled for this study and were randomly allocated into two groups. There were no drop outs or failed blocks. Group C received bupivacaine with clonidine and Group D received bupivacaine with dexmedetomidine for supraclavicular brachial plexus nerve block. There were no statistically significant differences in the demographic characters and duration of surgery between the two groups. The time of onset of sensory block was 6.85 ±2.27 minutes in Group D but in Group C was 10.17 ± 1.65 minutes and it was statistically highly significant (p value < 0.001). Onset of motor block in Group D was 9.10 ± 2.83 minutes but in Group C was 12.52 ± 1.37

minutes and it was statistically highly significant (p value < 0.001). Time to rescue analgesic was longer in Group D than Group C. For Group D it was 894.75 ± 63.30 minutes and for Group C 606.75 ± 22.17 minutes. This difference was statistically highly significant (p value < 0.001). Patients in both groups were sedated and easily arousable. In Group D, 9 patients developed bradycardia and 5 patients developed hypotension but in group C, 2 patients developed bradycardia and 2 patients developed hypotension. For bradycardia it was statistically significant (p value <0.05).

Discussion

Surgical pain is a universal phenomenon, affecting all patients in the perioperative period, causing several deleterious effects on the patient's body physically and mentally. In fact the apprehension of post surgical pain sometimes overpowers the fear of surgery in patients and their relatives. It, therefore, becomes the moral responsibility of perioperative physicians like anaesthesiologists and surgeons to provide adequate postoperative analgesia not only to suppress the adverse physiological responses to pain, but also to improve the quality of patient care following the surgery. Regional nerve block can provide effective surgical anaesthesia as well as postoperative analgesia. Moreover, regional nerve block avoids the unwanted effects of the anaesthetic drugs used during general anaesthesia and the stress of laryngoscopy and tracheal intubation. Supraclavicular brachial plexus nerve block is a popular and widely employed regional nerve block technique for perioperative anaesthesia and analgesia for surgery of upper extremity. Local anaesthetics alone for supraclavicular brachial plexus block provide good operative condition but have shorter duration of postoperative analgesia. So, various drugs, as adjuvant, were used with local anaesthetics in brachial plexus block to achieve quick, dense and prolonged block. Recent data suggest that, with the complexity of neurotransmitters responsible for nociception both at the peripheral and at the central level, it may be necessary to use combinations of adjuncts to achieve maximal benefit with minimal adverse effects. [8] The aim of our study was to evaluate and compare whether additional anaesthetic and analgesic effects could be achieved from administration of α2 adrenoceptor agonists, clonidine and dexmedetomidine as a adjuvant in brachial plexus nerve block. Our study was a prospective, randomized, double-blind study carried out at the Department of Anaesthesia at Bankura Sammilani Medical College & Hospital, Bankura. Eighty ASA I and II patients undergoing elective upper limb orthopedic surgery were included in our study. Patients were divided into 2 equal groups [Group C and Group D] randomly by lottery method and each group had 40 patients each. Group C patients

received 38 ml of 0.25% bupivacaine and 1µg/kg body weight clonidine. Group D patients received 38 ml of 0.25% bupivacaine and 1µg/kg body weight dexmedetomidine. It is well known that in peripheral myelinated and nonmyelinated fibers, membrane hyperpolarization develop that can produce sensory effects and pain during or after stimulation and it is mainly due to the activation of the sodium-potassium pump after the transient influx of sodium ions.[9] **Dalle et al**.[10] found that clonidine enhances the sensory blockade by blocking the inhibiting hyperpolarization activated cation current to enhance the level of hyperpolarization and thus inhibits subsequent action potentials. **Singelyn et al.** reported that the use of clonidine in peripheral nerve blocks is safe and beneficial.[11,12] **Esmaoglu et al**.[13], **Kaygusuz et al**.[14] **and Rancourt et al**.[15] showed that dexmedetomidine was safe when used as an addition to local anaesthetic for brachial plexus block and posterior tibial nerve sensory blockade. **Esmaoglu et al**.[13] and **Kaygusuz et al**.[14] also showed that when dexmedetomidine is used as an addition to local anaesthetic, it can provide faster onset and longer duration for brachial plexus block, but resulted in some side effects, such as hypotension and bradycardia. Although dexmedetomidine has an α_2/α_1 selectivity ratio that is eight times higher than that of clonidine, an equipotent comparative study of both the drugs in peripheral nerve block was not available at the time of our study. The dose selection was based on previous studies where dexmedetomidine 1 µg/kg and clonidine 1 µg/kg were used in Bier's block as an adjuvant to lignocaine.[16]. In our study, we compared the addition of clonidine (Group C 1 µg/kg) and dexmedetomidine (Group D 1 µg/kg) to bupivacaine in supraclavicular brachial plexus nerve block. The result of our study shows that all patients in both groups were comparable with respect to demographic profile, duration of surgery. **Esmaoglu et al**. added dexmedetomidine to levobupivacaine for axillary brachial plexus block and showed that it shortens the onset time of both sensory and motor block, prolongs the duration of block and the duration of postoperative analgesia.[17] This may be because peripheral α_2 agonist produces analgesia by reducing release of norepinephrine, leading to α_2 receptor-independent inhibitory effects on nerve fiber action potentials.[17, 18] In our study we found that onset of sensory block was faster in Group D (6.85±2.27 minutes) compared to Group C (10.17±1.65 minutes) and this was statistically highly significant (p value <0.001). Onset of motor block was also faster in Group D (9.10 ± 2.83 minutes) compared to Group C (12.52 ± 1.37 minutes) and it was staistically highly significant. **Chakraborty et al.** found that when clonidine added to bupivacaine was used for supraclavicular brachial plexus block, onset of sensory and motor block was faster than the control group and in clonidine group, sensory block was more rapid than motor block. [19] Though, **Gandhi et al.** in their study

observed that onset of motor block was faster than sensory block when they used dexmedetomidine as adjuvant to bupivacaine for brachial plexus block.[20] This may be explained by "core and mantle" concept of **Winnie et al.,** which states that outer motor fibers of brachial plexus form the mantle and are blocked earlier than the sensory fibers at the core. That's why onset of motor blockade was significantly faster than sensory block.[21] **Kaygusuz et al.** showed that when dexmedetomidine was added to local anaesthetics, it provides faster onset in brachial plexus block.[22] **Lin et al.** reported that dexmedetomidine has a double effect, playing an anticentral sympathetic role and activating the vagus nerve to lower plasma catecholamine levels which can lower blood pressure (BP) and heart rate (HR), providing stable haemodynamics. However, it also has a dose-related inhibition for BP and HR.[23] In our study we found that heart rate was consistently lower in Group D and this was statistically highly significant at 10, 15, 30, 45 and 60 minutes [p<0.001]. Nine out of 40 patients in group D developed bradycardia in comparison to 2 out of 40 patients in group C where pulse rate below 60 beats per minutes but not less than 55 beats per minutes and it was statistically significant. Systolic, diastolic and mean arterial pressures were comparable in both groups at all time points except diastolic blood pressure at 15, 30, 45 and 60 minutes and mean arterial pressure at 30 minutes were lower in Group D and it was statistically significant. This finding is corroborated with study done by **Sandhya Agarwal et al.** They found that except for the initial recordings (at 0, 5, 10, and 15 min), heart rate levels in group SD were significantly lower ($P < 0.001$). SBP and DBP levels in SD group at 15, 30, 45, 60, 90 and 120 min were significantly lower than in S group ($P < 0.001$). In fact, when the percentage changes in HR/SBP/DBP were compared from 0-5/0-10/0-15/0-30/0-45/0-60/0-90/0-120 min in SD with S group, they came out to be highly significant ($P < 0.001$) in group SD.[5] **Lin et al.** also reported that heart rate was lower in dexmedetomidine group than control group.[23] In our study we found that sedation score in Group D was higher and the difference was statistically significant. All the patients in both groups were sedated and easily arousable. **Swami et al.** in their study found that patients in dexmedetomidine group did not require any sedation intraoperatively and they were comfortable throughout the surgery with arousable sedative effects.[24] This can be explained on the basis that some amount of systemic absorption of drug could be present.[25] As α_2 agonists produce sedation by central action, they produce inhibition of substance P release in the nociceptive pathway at the level of the dorsal root neuron and by activation of α_2 adrenoreceptor in locus ceruleus. **Lin et al.** also found that the patients who received dexmedetomidine in cervical plexus block were sedated and arousable. According to them it is due to systemic effect that is caused by tissue

capillary reabsorption and its direct effect on the peripheral nerves.[23] **Chakraborty et al.** found that the patients who received clonidine were more sedated.[19] **Singh et al.** reported that sedation, which is often associated with clonidine, was not apparent in their study.[26] In our study we found that there was statistical significant difference in SpO_2 between two groups at 10, 15 and 45 minutes peroperative periods though all the patients in both groups maintained SpO_2 >98%. **Chakraboty et al.** was found that no statistical significant difference in respect to saturation of oxygen (SpO2) in the two groups at any time point.[19] In our study, post operative VAS score was lower in group D in compared to group C. VAS score at 6 hours in Group D was (1.10 ± 0.52) but in Group C was (2.27 ± 0.45) and VAS score at 12 hours in Group D was (2.40 ± 0.63) but in Group C was (5.85 ± 0.80) and this was highly significant (p value <0.001). At 24 hours VAS score in two groups were 10. Time to rescue analgesic requirement was longer in Group D than Group C. For Group D it was (894.75±63.30 minutes) and for Group C (606.75 ± 22.17 minutes). This difference was statistically highly significant (p value <0.001). This finding corroborates with the study by **Swami et al**.[24] (for Group D 456.21 ± 97.99 minutes; for Group C 289.67 ± 62.5 minutes which was statistically significant). **Abdallah et al.** reviewed that there was an increase in time to first analgesic request by 345 minutes in the dexmedetomidine group as compared to local anaesthetics alone.[27]

There were no statistically significant differences between two groups in respect to postoperative heart rate, blood pressure, sedation score except SpO_2 in which there is significant difference at 0 and 2 hours though all the patients in both groups maintained saturation above 98%. None of the patients required additional oxygen at post anaesthesia care unit. None of the patients developed respiratory depression. And also in our study, in Group D, 9 patients developed bradycardia and 5 patients developed hypotension but in Group C, 2 patients developed bradycardia and 2 patients developed hypotension. Patients in Group D developed more bradycardia and it was statistically significant (p value 0.023). Hypotension also was more in patients of Group D but it was statistically insignificant (p value 0.235). The observed bradycardia was transient, successfully reversed by intravenous atropine administration, and did not recur later during the postoperative period. This finding is corroborated with the meta analysis done by **Abdallah et al**.[27] and **Esmaoglu et al**.[13] who also found bradycardia in dexmedetomidine group when they used it in axillary brachial plexus block. In their study 8 patients out of 30 patients developed bradycardia. **Lin et al.** in their study observed bradycardia in 2 patients out of 20 patients. They hypothesized that this difference might be due to individual sensitivity to dexmedetomidine.[23] **Bernard et al.**

reported the incidence of hypotension and bradycardia with the use of clonidine.[28] The limitations of our study were that we did not use ultrasound guided blocks because of unavailability at the time of our study; this could have helped us to lower dosages and volumes of local anaesthetic. From our study, we would like to suggest that dexmedetomidine can be safely used as an adjuvant to local anaesthetic in peripheral nerve blocks.

Conclusion

Dexmedetomidine (1µg/Kg) when added as adjuvant to bupivacaine (0.25%) in supraclavicular brachial plexus nerve block, enhanced the onset of sensory and motor block when compared with clonidine (1 µg/Kg). The time for rescue analgesic requirement was prolonged in patients receiving dexmedetomidine when compared to clonidine. Perineural dexmedetomidine produces some side effects (hypotension, bradycardia) more than clonidine but these can be reversed easily by appropriate medication. Side effects may be associated with dosage or individual sensitivity. To conclude, we would like to suggest that dexmedetomidine can be safely used as an adjuvant to local anaesthetic in peripheral nerve blocks.

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