Volume-5, Issue-3, March - 2016 • ISSN No 2277 - 8160 IF : 3.62 | IC Value 70.36

Research Paper Medical Science

Dexmedetomidine And Clonidine (A2 Agonist Drugs) As An Adjuvant To Local Anesthesia in Supraclavicular Brachial Plexus Block: A Comparative Randomized Double-Blind Prospective Study

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ABSTRACT

Background and Objectives: Alpha-2 agonists are mixed with local anesthetic agents to extend the duration of spinal, extradural and peripheral nerve blocks. We compared clonidine and Dexmedetomidine as an adjuvant to levobupivacaine in supraclavicular brachial plexus block with respect to onset and duration of sensory and motor block and duration of analgesia. Methods: Sixty ASA I and II patients scheduled for elective upper limb surgeries under supraclavicular brachial plexus block were divided into two equal groups in a randomized, double-blinded fashion. Group A received clonidine 1 µg/kg and Group B received dexmedetomidine 1 µg/kg added to levobupivacaine 0.25% (35 cc). Onset and recovery time of sensory and motor block, duration of analgesia and quality of block were studied in both the groups. Results: Duration of sensory block and motor block was 292.67±59.13 and 227.00±48.36 min, respectively, in Group A, while it was 472.24±90.06 and 413.97±87.13 min, respectively, in Group B. There was no statistically significant difference in onset of sensory and motor block between the two groups. The number of patients achieving grade IV quality (excellent) of block was higher in Group B (80%) as compared with Group A (40%) (P<0.05).Conclusion: Dexmedetomidine when added to levobupivacaine in supraclavicular brachial plexus block enhanced the duration of sensory and motor block. The time for rescue analgesia was prolonged in patients receiving dexmedetomidine. It also enhanced the quality of block as compared with clonidine.

KEYWORDS : Levobupivacaine, Clonidine, dexmedetomidine, supraclavicular block

INTRODUCTION:

Upper limb surgeries are mostly performed under peripheral blocks such as the brachial plexus block. Peripheral nerve blocks not only provide intraoperative anesthesia but also extend analgesia in the post-operative period without any systemic side-effects.[1]

There has always been a search for adjuvants to the regional nerve block with drugs that prolong the duration of analgesia but with lesser adverse effects. The search for the ideal additive continues, and led us to try the novel α2 adrenergic agent, dexmedetomidine.

Alpha-2 adrenergic receptor agonists have been the focus of interest for their sedative, analgesic, perioperative sympatholytic and cardiovascular stabilizing effects with reduced anesthetic requirements.

Dexmedetomidine, a potent α_2 adrenoceptor agonist, is approximately eight-times more selective towards the α_2 adrenoceptor than clonidine. [2] In previous clinical studies, intravenous dexmedetomidine resulted in significant opioid sparing effects as well as a decrease in inhalational anesthetic requirements. [3] In humans, dexmedetomidine has also shown to prolong the duration of block and post-operative analgesia when added to local anesthetic in various regional blocks. [4],[5],[6],[7] The current study was designed to test the hypothesis that dexmedetomidine when added as an adjuvant to levobupivacaine in supraclavicular brachial plexus block enhanced the duration of sensory and motor block as compared with clonidine.

METHODS:

After ethical committee approval and written informed consent, a double-blind randomized prospective clinical study was carried out on 60 American Society of Anesthesiologist (ASA) Grade I and II patients of either sex, aged 18-50 years, undergoing various bony orthopedic surgeries on the upper limb under brachial plexus block with supraclavicular approach. The study was conducted in two groups of 30 patients each. The patients were randomly assigned using "slips in a box technique" to one of the following groups:

GroupA:

Levobupivacaine 0.25% (35 cc) + clonidine 1 µg/kg

Group B:

Levobupivacaine 0.25% (35 cc) + dexmedetomidine 1 µg/kg

Patients on adrenoreceptor agonist or antagonist therapy, with known hypersensitivity to local anesthetic drugs, bleeding disorders, uncontrolled diabetes mellitus, pregnant women and pre-existing peripheral neuropathy, were excluded from the study.

On arrival in the operation room, baseline heart rate, blood pressure and oxygen saturation were recorded. An intravenous line with 18 G cannula was secured in the unaffected limb and Ringer's lactate was started.

All the patients received brachial plexus block through the supraclavicular approach by an experienced anesthesiologist different from the one assessing the patient intra- and post-operatively. Both were blinded to the treatment groups. Neural localization was achieved by using a nerve locator connected to a 22 G, 50-mm-long stimulating nee-

dle. The location end point was a distal motor response with an output lower than 0.2 mA in the median nerve region.

After checking for negative aspiration to blood, 35 mL of a solution containing local anesthetic combined with clonidine or dexmedetomidine as mentioned above was injected. A 3-min massage was performed to facilitate an even drug distribution. A band of local anesthesia was given with 5ml of 0.125 % levobupivacaine plain in the medial aspect of upper one third of arm to facilitate the block of intercostobrachial nerve to prevent discomfort due to tourniquet application.

Sensory block was assessed by the pin prick method. Assessment of sensory block was done at each minute after completion of drug injection in the dermatomal areas corresponding to median nerve, radial nerve, ulnar nerve and musculocutaneous nerve till complete sensory blockade. Sensory onset was considered when there was a dull sensation to pin prick along the distribution of any of the above-mentioned nerves. Complete sensory block was considered when there was complete loss of sensation to pin prick.

Sensory block was graded as-

Grade 0: Sharp pin felt

Grade 1: Analgesia, dull sensation felt

Grade 2: Anesthesia, no sensation felt.

Assessment of motor block was carried out by the same observer at each minute till complete motor blockade after drug injection. Onset of motor blockade was considered when there was Grade 1 motor blockade. Peak motor block was considered when there was Grade 2 motor blockade. Motor block was determined according to a modified Bromage scale for upper extremities on a 3-point scale.

Grade 0: Normal motor function with full flexion and extension of elbow, wrist and fingers

Grade 1: Decreased motor strength with ability to move the fingers only

Grade 2: Complete motor block with inability to move the fingers

The block was considered incomplete when any of the segments supplied by median, radial, ulnar and musculocutaneous nerve did not have analgesia even after 30 min of drug injection. These patients were supplemented with intravenous fentanyl (1 µg/ kg) and midazolam (0.02 mg/kg). When more than one nerve remained unaffected, it was considered a failed block. In this case, general anesthesia was given intraoperatively. Patients were monitored for hemodynamic variables such as heart rate, blood pressure and oxygen saturation every 30 min after the block intraoperatively and every 60 min post-operatively. Sedation of patient was assessed by the Ramsay Sedation Score. At the end of the procedure, quality of operative conditions were assessed according to the following numeric scale :

Grade 4: (Excellent) No complaint from patient

Grade 3: (Good) Minor complaint with no need for the supplemental analgesics

Grade 2: (Moderate) Complaint that required supplemental analgesia

Grade 1: (Unsuccessful) Patient given general anesthesia

Assessment of blood loss was done and fluid was administered as per the loss. Duration of surgery was noted.

The intra- and post-operative assessment was done by an anesthesiologist who was unaware of the drug used. The rescue analgesia was given in the form of inj. Diclofenac sodium (1.5 mg/kg) intramuscularly. All patients were observed for side-effects like nausea, vomiting, dryness of mouth and complications like pneumothorax, hematoma, local anesthetic toxicity and post-block neuropathy in the intra- and post-operative periods.

The duration of sensory block was defined as the time interval between the onset of analgesia and the complete resolution of anesthesia on all nerves. The duration of motor block was defined as the time interval between the onset of paresis and the recovery of complete motor function of the hand and forearm.

Statistical analysis

the data was analyzed by student's unpaired t-test. Unpaired t-test was applied for demographic data, hemodynamic parameters, onset and duration of sensory and motor blockade. Fisher exact test was applied for assessment of quality of block. *P*-value was considered significant if <0.05 and highly significant if <0.001.

RESULTS:

Eighty patients posted for upper limb surgeries were assessed for suitability to enroll in the study. Six patients were not interested to participate in the study. Five patients were excluded as they were posted for soft tissue surgeries of the upper limb. Nine patients were excluded as they were found to be on beta blockers, anticoagulation drugs and had uncontrolled diabetes mellitus. The remaining 60 patients fulfilling the inclusion criteria were randomly assigned to one of the two groups.

Both groups were comparable in terms of age, gender, weight and type of surgeries [Table 1] (*P*>0.001).

TABLE 1: Patient Characteristics

Parameters	Group A	Group B	P Value
Age (years)	32.74±12.08	33.12±15.64	NS
Weight (kg)	57.3±5.1	53.43±7.84	NS
Gender (M/F)	21/9	18/12	NS
Type of surgeries Fracture radius ulna Fracture olecranon Fracture lower end of humerus	 13 10 7	 14 9 7	

The baseline hemodynamic parameters were comparable in both groups. Significantly lower pulse rate was observed at 60, 90 and 120 min, but not less than 60 beats/min, in Group B as compared with Group A [Figure 1] (*P*<0.001). Systolic and diastolic blood pressure were found to be significantly lower than baseline from 30 to 120 min in Group B as compared with Group A (Graph II) (*P*<0.001). No treatment was required for this fall in blood pressure. The hemodynamic parameters were comparable at the end of 180 min. [Figure 2].

Figure 1: Comparison of pulse rate in both the group

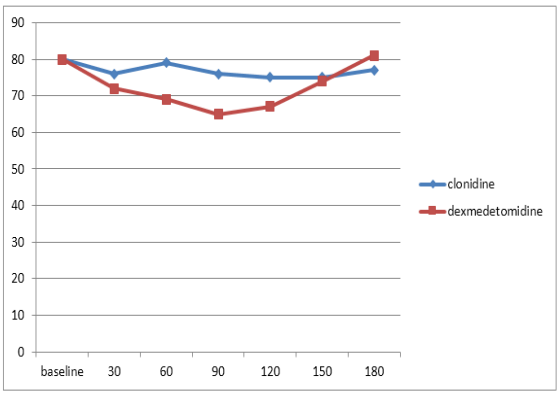
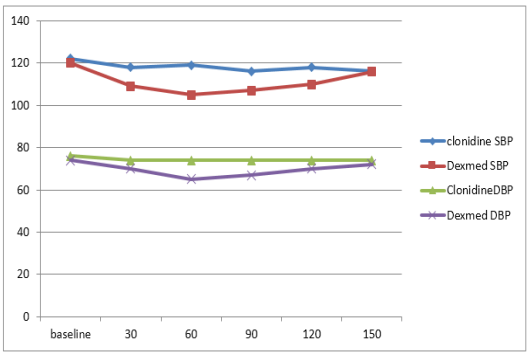


Figure 2: Comparison of systolic and diastolic blood pressure in both the groups

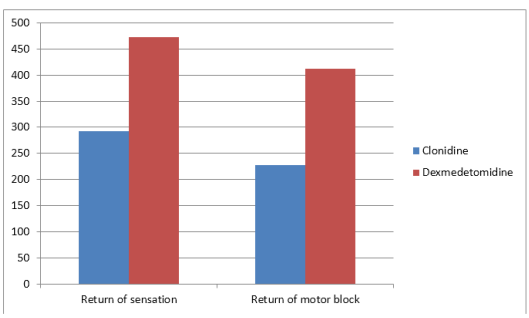


Onset of sensory block was faster in Group B than in Group A, while onset of motor block was faster in Group A than in Group B, but the difference was not statistically significant [Table 2] (*P*>0.001).

TABLE 2: Sensory and motor block onset time and durations in both groups

	Group A	Group B	P Value
Onset time of sensory block (min)	2.32±1.22	1.76±1.29	P<0.01
Onset time of motor block (min)	3.84±1.82	4.64±2.45	P<0.1
Duration of sensory block (min)	292.68±58.23	472.24±90.42	P<0.0001
Duration of motor block(min)	228.12±47.47	412.12±87.27	P<0.0001

Figure 3 : Comparison of duration of sensory block, motor block in both the groups



Duration of sensory block was 292.68 min in Group A s compared with 472.24 min in Group B. Statistically significant longer duration of sensory block was observed in Group B [Table 2] and [Figure 3] (*P*=0.001).

The duration of motor block was 228.12 min in Group A as compared with 412.12 min in Group B. Again, duration of motor block was significantly longer in Group B [Table 2] and [Figure 3] (*P*=0.001)

In Group B, 83.3% of the patients achieved Grade IV quality of block as opposed to 43.3% in Group A (*P*<0.05). There were a total 18 patients in Group A with Grade II and III block and seven patients in Group B who required sedation or sedation with analgesia. One patient in Group A required general anesthesia as the block was inadequate [Table 3].

Table 3: Quality of Block

Grade	Group A (%)	Group B (%)	P value
I	1(3.3)	-	0.015
II	8(26.7)	2(6.7)	0.03
III	8(26.7)	3(10)	0.01
IV	13(43.3)	25(83.3)	0.001

No side-effects (nausea, vomiting, dry mouth) were reported during the first 24 h in the post-operative period in both the groups.

Discussion:

In this randomized, double-blinded trial, we compared dexmedetomidine and clonidine (α_2 agonist) as an adjuvant to levobupivacaine in supraclavicular brachial plexus block, and found that there was a significantly increased duration of sensory and motor blockade in the dexmedetomidine group than in the clonidine group without any adverse effects.

Peripheral action of clonidine

Clonidine was initially used for its antihypertensive properties. The central actions are mediated through α_2 adrenoceptors, which are situated at locus coeruleus and dorsal horn of spinal cord. But, specific peripheral effects of clonidine appear to be less obvious because α_2 adrenoceptors are not present on the axon of the normal peripheral nerve. [8]

There have been four proposed mechanisms for the action of clonidine in peripheral nerve blocks. They are

1. Centrally mediated analgesia

2.α_2 adrenoceptor-mediated vasoconstrictive effects,

3. Attenuation of inflammatory response and

4. Direct action on peripheral nerve. [9]

The direct action of clonidine on the nerve can be explained on the basis of a study conducted by Dalle *et al*. They proposed that clonidine, by enhancing activity-dependent hyperpolarization generated by the Na/K pump during repetitive stimulation; increase the threshold for initiating the action potential causing slowing or blockage of conduction. [10] Kosugi *et al*. examined the effects of various adrenoceptor agonists including dexmedetomidine, tetracaine, oxymetazoline and clonidine, and also an α_2 adrenoceptor antagonist (atipamezole) on compound action potential (CAP) recorded from frog sciatic nerve, and found that CAPs were inhibited by α_2 adrenoceptor agents so that they are able to block nerve conduction. [11]

Popping *et al*. in their met analysis of randomized trials showed that the beneficial effect of clonidine on the duration of analgesia was observed with all tested local anesthetics. They observed that the prolongation of motor block was higher when clonidine was added to bupivacaine as compared with Ropivacaine. The least effect was noted with Prilocaine. [8]

Peripheral action of dexmedetomidine

Dexmedetomidine and clonidine are both α_2 selective agonists. It is possible that they work in a similar manner and may indicate a class effect.

A study by Brumett *et al*. showed that dexmedetomidine enhances duration of bupivacaine anesthesia and analgesia of sciatic nerve block in rats without any damage to the nerve. The histopathological evaluation of these nerve axons and myelin were normal in both control and dexmedetomidine + bupivacaine groups. [9]

In an another study, per neural dexmedetomidine added to Ropivacaine for sciatic nerve block in rats prolonged the duration of analgesia by blocking the hyperpolarization-activated cation. This effect was reversed by a hyperpolarisation-activated cation channel enhancer but not by an α_2 adrenoreceptor antagonist. This shows that the analgesic effect of peripheral per neural dexmedetomidine was caused by enhancement of the hyperpolarization-activated cation current, which prevents the nerve from returning from a hyperpolarized state to resting membrane potential for subsequent firing. [12]

Kousugi *et al*. in their study found that high concentrations of dexmedetomidine inhibit CAPs in frog sciatic nerves without $\alpha_2$adrenoceptor activation. Their result showed that dexmedetomidine reduced the peak amplitude of CAPs reversibly and in a concentration- dependent manner. This action was not antagonized by α_2 adrenoceptor antagonists (i.e., yohimbine and atipamezole); rather, α_2 antagonists reduced the CAP peak amplitude. Clonidine and oxymetazoline, two other α_2 agonists, also inhibit CAPs. The maximum effect of clonidine was only 20%. On the other hand, adrenaline, noradrenaline and α_1 agonist phenylephrine and beta agonist isoprenaline had no effect on CAPs. [11]

The efficacy of peripheral per neural dexmedetomidine added to bupivacaine and Ropivacaine for sciatic nerve blocks in rats has been established. [13], [12] the increase in duration of analgesia is dose dependent [13] and the effect is peripheral (i.e., not caused by centrally mediated or systemic analgesia). [12] However all studies carried out so far to prove the peripheral action of α_2 agonists were animal studies only. There are very few human studies, i.e. greater palatine and axillary brachial plexus nerve blocks have subsequently demonstrated that increased duration of sensory blockade can be achieved by adding dexmedetomidine to bupivacaine and levobupivacaine, respectively.[14],[15] Keeping these facts in mind, we decided to compare the action of two α_2 agonists, i.e. clonidine and dexmedetomidine with levobupivacaine in lesser concentration (0.25%), in peripheral nerve blocks so that by increasing the duration of analgesia with a single shot block we can achieve a longer duration of post-operative analgesia without significant clinical side-effects and hence we can avoid continuous catheterization.

Singelyn *et al*. reported that a minimum dose of clonidine (0.5 µg/kg) added to mepivacaine prolongs the duration of anaesthesia and analgesia after brachial plexus block. No added benefits were found with doses exceeding 1.5 µg/kg. The enhancing effect of a small dose of clonidine on lignocaine may be because of the evoked inhibition of C-fiber action potential. Therefore, we decided to use clonidine at a dose of 1 µg/kg in our study. [16]

In our study, we compared the addition of clonidine (Group A 1 µg/kg) and dexmedetomidine (Group B 1 µg/kg) to levobupivacaine in supraclavicular brachial plexus block. The result of our study shows that all patients in both groups were comparable with respect to demographic profile, duration of surgery and type of surgery. With these doses, we had stable hemodynamics in patients except significant lower pulse rate in Group B at 60, 90 and 120 min as compared with Group A, but not less than 60 beats/min.

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 post-operative analgesia. [14]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. [14],[15] However, in our study, we found that onset of sensory block was a little faster with Group B as compared with Group A, but it was statistically insignificant, while onset of motor block was a little longer in Group B but again not significant statistically. The duration of analgesia in Group B was longer than in Group A, and it was statistically significant.

The concern of prolongation of motor block was minimal patient discomfort on movement in the post-operative period.

None of the patients in Group B required sedation intraoperatively and they were comfortable throughout the surgery with arousable sedative effects. This can be explained on the basis that some amount of systemic absorption of drug could be present. [8] 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 coeruleus. [17]

From this study, we would like to suggest that dexmedetomidine can be safely used with local anesthetic in peripheral nerve blocks; however, further trials to determine the exact dose and effect of neurotoxicity on the human nerve are required.

Conclusion:

To conclude, we would like to state that dexmedetomidine prolongs the duration of sensory and motor block and enhances the quality of block as compared with clonidine when used as an adjuvant to levobupivacaine in supraclavicular brachial plexus block.

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