

## Comparison of low dose dexmedetomidine and clonidine as additives to bupivacaine in ultrasound directed supraclavicular blocks

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### Abstract

**Introduction:** Ultrasound guidance has resulted in a renewal of interest in supra clavicular approach of brachial plexus block for surgeries below the shoulder. There is a necessity for an additive that increase the duration of local anaesthetics providing effective postoperative analgesia also after one shot injections. Dexmedetomidine and clonidine are the common adjuvants used, but in higher doses. The aim of this study was to see which among them is a better analgesic additive in lower doses.

**Materials and Methods:** Sixty patients, aged 18-55 years, posted for hand and forearm surgeries under Ultrasound directed supraclavicular brachial block were divided randomly in to 2 groups using computer generated tables.

**Group C:** Clonidine 0.5 µg /kg added to 25ml of 0.375% bupivacaine.

**Group D:** Dexmedetomidine 0.5 µg /kg and 25ml of 0.375% bupivacaine.

The onset and the duration of analgesia, motor block and sedation scores were noted.

**Results:** Onset of sensory block was 11.6 +/-3.4 minutes in group C, 14.4 +/-4.5 minutes in group D. The onset of motor block was 17.6 +/-4.9 in group C, 20.6 +/-5.9 in group D. The mean time of sensory block in Group C was 9.7 +/-1.6 hours, 13.3 +/-1.9 hours in Group D. Motor blockade (hrs) was for 9.1 +/-1.7 in Group C, 12.1 +/-2.0 in Group D. Analgesia and motor blockade were longer in dexmedetomidine group. Rescue analgesic was given at 10.5 ± 1.7 hrs in clonidine category and at 15 ± 2.2 hrs in dexmedetomidine category. 10% of subjects in Dexmedetomidine category had adverse reactions, it was not there in clonidine.

**Conclusions:** Dexmedetomidine showed features of a superior additive compared to clonidine as it enhanced the quality and duration of analgesia with lesser complications at lower doses.

**Keywords:** Bupivacaine, Dexmedetomidine, Clonidine, Ultrasound, Supraclavicular brachial plexus block.

### Introduction

Supraclavicular brachial blocks provide ideal operative conditions for upper limb procedures. Ultrasound imaging has increased the safety of this procedure due to excellent visibility of anatomy and needle passage. Various drugs have been used as adjuvants to improve the block. Bupivacaine is the commonest local anaesthetic<sup>1</sup> used due to prolonged action (4-8 hours).

It is proven that additives like clonidine and dexmedetomidine when added to bupivacaine during a single-shot plexus block prolongs the duration of action.<sup>2</sup> But the requirement of higher volume and concentration of local anaesthetics as well as adjuvants decreases the safety margin in paraesthesia and blind technique. Blocks using peripheral nerve stimulator also can cause injury to nerves and vascular structures.<sup>5</sup> Recently, the use of USG guidance has increased success and the safety along with marked reduction of the dose of local anaesthetics and adjuvants.<sup>7</sup> Higher doses of alpha 2 agonist are associated with hypotension and bradycardia especially in patients on cardiac medications.<sup>23</sup> Hence we decided to compare the efficacy of low dose adjuvants like clonidine and dexmedetomidine in USG guided supraclavicular block

Dexmedetomidine is a dextro-enantiomer and active component of medetomidine<sup>3</sup> approved as intravenous sedative and co analgesic drug. Its alpha2/alpha1 selectivity ratio is 8 times than that of clonidine.<sup>4</sup> Clonidine and

dexmedetomidine as additive to bupivacaine are investigated for blind brachial plexus block. Very few studies have so far compared low dose of these additives.

### Materials and Methods

**Source of Data:** After Institutional ethical committee approval and written informed consent, 60 patients, aged 18-55 years ASA Grade I & II, posted for upper limb surgery under ultra sound guided supraclavicular brachial plexus block were included in this prospective randomized double blind study.

#### Exclusion Criteria

1. Patient refusal
2. Patients with pre-existing neurological disorders (peripheral neuropathy or motor weakness).
3. Known history of hypersensitivity to drug
4. Inadequate block
5. History of coagulopathy or anti-coagulant medication intake

Patients were randomly allocated to either of the 2 groups using a computer generated randomisation table. Drug solutions were prepared by an investigator not involved in performing or assessing the characteristics of the block and handed over to anaesthetist performing the block. The anaesthesiologists performing and observing the block characteristics were blinded to treatment groups. The

procedure was conducted by a consultant in the department with one year experience in USG guided blocks.

**Group C:** Clonidine 0.5 µg/kg added to 25ml of 0.375% bupivacaine.

**Group D:** Dexmedetomidine 0.5 µg/kg and 25ml of 0.375% bupivacaine.

After shifting the patients to O.T, intravenous access was secured on opposite limb and crystalloid infusion was started. Baseline haemodynamic parameters recorded. Brachial block was carried out under USG guidance under strict aseptic precautions. The block was achieved with 25ml of 0.375% bupivacaine combined with clonidine or dexmedetomidine. Our pilot study with 0.25% bupivacaine failed to provide complete motor block which was required for prolonged surgeries. So we decided for 0.375% bupivacaine.

Dermatomes of Median nerve, radial nerve, ulnar nerve and musculocutaneous nerve were checked for sensory block. Dull sensation to pin prick was noted as the onset of sensory block.<sup>29</sup>

Loss of sensation was marked as

Grade 0: Sharp pin felt

Grade 1: Analgesia, dull sensation felt

Grade 2: Anaesthesia, no sensation felt.

Motor block was determined according to a modified Bromage scale for upper extremities on a 3-point scale.<sup>29</sup>

When any of the segments supplied by median, radial, ulnar and musculocutaneous nerve did not have analgesia even after 30 min of drug injection, those patients were exempted from the study and given general anaesthesia. Haemodynamic variables were recorded every 5 min intraoperatively and hourly in the postoperative period.

Duration of sensory and of motor block were recorded. Assessment of Sedation was done by the Ramsay Sedation Score.<sup>16,29</sup>

**Table 1: Demographic profile**

Parameter	Group C	Group D	P value
Age (years) Mean±SD	31.1 +/-11.3	31.5+/-10.2	0.905 NS
Sex ratio (male/female)	25:5	25:5	1.00 NS
Weight (Kg) Mean±SD	62.5+/-6.9	64.9+/-6.7	0.168 NS
ASA I/II	28/2	29/1	0.5536

NS- Not significant, S- significant

**Table 2: Onset, duration of anesthesia and First rescue between two groups**

Block Characteristics	Group		P value
	Clonidine	Dexmedetomidine	
	Mean ± SD	Mean ± SD	
Onset of sensory (min)	11.6 ± 3.4	14.4 ± 4.5	0.008*
Onset of motor (min)	17.6 ± 4.9	20.6 ± 5.9	0.036*
Duration of sensory (hrs)	9.7 ± 1.6	13.3 ± 1.9	<0.001*
Duration of motor (hrs)	9.1 ± 1.7	12.1 ± 2.0	<0.001*
First rescue (hrs)	10.5 ± 1.7	15.0 ± 2.2	<0.001*

Onset and duration of sensory and motor block.

### Statistics for the Study

In order to detect a difference of 179 mins in duration of motor and sensory block, with 80% power and 5% level of significance a sample size of 30 per group were chosen<sup>17</sup>(Swami et al).

Data was analysed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Continuous data was represented as mean and SD. Independent t test was used as test of significance to identify the mean difference between two groups. Paired t test was the test for paired data such as before and after surgery. p value<0.05 was considered as statistically significant.

### Results

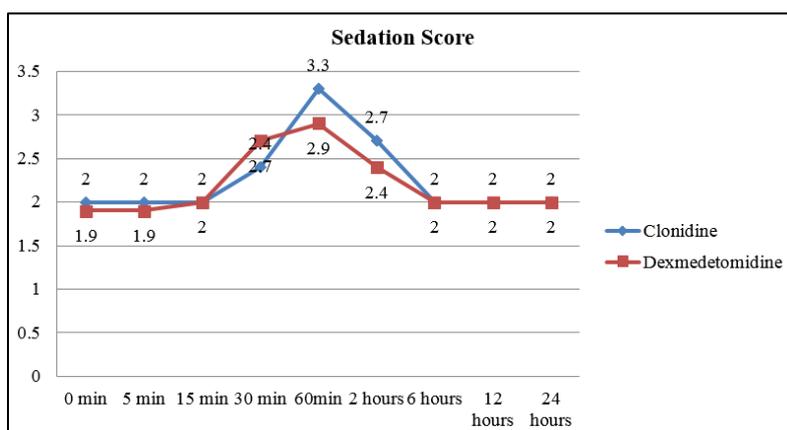
Thirty patients were enrolled in each group. Total of 60 patients were included. Both the groups were comparable with respect to age, weight, sex ratio and ASA physical status (Table 1).

The onset of sensory and motor block was faster in Group C (Clonidine group) than in Group D (Dexmedetomidine group) Table 2. The difference was not statistically significant (Clonidine group). The duration of sensory and motor block was longer in Group D compared to Group C. This difference was statistically significant (P<0.001) Table 2. Time for first rescue analgesic requirement was longer in dexmedetomidine group than clonidine group. (P<0.001) Table 2. Variation in sedation score was obtained at 0 and 60 minutes. Greater scores were noted in clonidine group than in dexmedetomidine group. Though the difference was statistically significant. (Table 3)

**Table 3: Comparison of sedation scores between two groups**

Sedation Score	Group						P value
	Clonidine			Dexmedetomidine			
	Mean	Median	SD	Mean	Median	SD	
0 min	2.0	2	0	1.9	2	0.3	0.04*
5 min	2.0	2	0	1.9	2	0.3	0.078
15 min	2.0	2	0	2.0	2	0.2	0.317
30 min	2.4	2	0.7	2.7	2	1.0	0.154
60 min	3.3	3	0.8	2.9	3	1.0	0.046*
2 hours	2.7	2	1.1	2.4	2	0.9	0.288
6 hours	2.0	2	0	2.0	2	0	1.000
12 hours	2.0	2	0	2.0	2	0	1.000
24 hours	2.0	2	0	2.0	2	0	1.000

variation in sedation score were observed at 0 min and at 60 min.



**Fig. 2: Bar diagram showing sedating score between two groups**

**Discussion**

Brachial plexus blocks provide good operative conditions and postoperative pain relief in upper limb surgeries. Bupivacaine alone provides pain relief for 3-8 hours following a plexus block.<sup>4,6</sup> Insertion of indwelling catheters to provide infusion of local anaesthetic or by adding additives increase the duration of action. Catheter usage is limited because of issues in placement, failure rate, catheter dislodgement, problems with catheter removal or infection. Midazolam, neostigmine, and dexamethasone are studied in conjunction to local anaesthetics and have been tried as additives.

Alpha 2 adrenergic stimulants have been utilized for more than 100yrs. Routes of administration such as central neuraxial and peripheral neural injections have been done to increase the duration and improve the quality of anaesthesia. clonidine and dexmedetomidine are partial and selective alpha 2 agonist respectively.<sup>14</sup>

Recent introduction of Ultrasound guidance has established its effectiveness and safety and revolutionised the practice, it has improved the safety along with marked reduction in the dose of local anaesthetics and adjuvants.<sup>8</sup> USG helped us in seeing the nerve plexus and depositing the drug at the plexus.

The commonly missed area, above the first rib and inferomedial to the plexus and posterolateral to the

subclavian artery, could be visualized with Ultrasound and spread of the drug to this area and around the plexus could be confirmed.

In the previous studies, higher dose of adjuvants to local anaesthetics were used.<sup>17</sup> We chose 0.5µg/kg of dexmedetomidine and clonidine in order to assess the efficacy of lower dose adjuvants with ultrasound guidance and also to reduce the side effects if any.

There are not many studies comparing micro dose of α2 agonists as an additive to 0.375% bupivacaine using Ultrasound in brachial plexus block. Our study was done among sixty patients aged 18-55 years to select the better adjuvant among 0.5 µg/kg of clonidine and 0.5µg/kg of dexmedetomidine that can be used with 0.375% bupivacaine under USG guidance. These two groups were compared in terms of quality of sensory and motor block.

Patients fulfilling the inclusion criteria were grouped into either Group D or Group C according the computer-generated randomized tables. We chose 0.375% bupivacaine as our pilot study performed with 0.25% bupivacaine failed to provide complete motor block which was essential for the long surgical procedures. Sedative premedication was avoided to see sedation scores. Both groups were comparable with respect to demographic data. In this we saw that the mean onset of sensory block was 11.6 +/-3.4 minutes in group C and 14.4 +/-4.5 minutes in group D. The mean onset of

motor block was 17.6 +/-4.9 in group C and 20.6+/-5.9 in group D. This difference was statistically significant. The duration of sensory block was 9.7+/-1.6 hours in Group C and 13.3 +/- 1.9 in Group D. The duration of motor block 9.1+/-1.7 hours in Group C and 12.1+/-2 in Group D. Rescue analgesic was required at 10.5 +/- 1.7 hours in Group C and 15+/- 2.2 hours in Group D.

### Comparison of Onset of Sensory and Motor Blockade

Swami et al<sup>17</sup> in 2012 did a double blinded study in 60 ASA I and II patients who received nerve stimulator guided brachial plexus block to compare clonidine 1mcg/kg and dexmedetomidine 1mcg/kg added to 0.25% bupivacaine. In this study we found that the mean onset of sensory block was 11.6 +/-3.4 minutes in group C, 14.4 +/-4.5 minutes in group D. The onset of motor block was 17.6 +/-4.9 in group C and 20.6+/-5.9 in group D. The difference was statistically significant.

Jinjilet al<sup>20</sup> 2015 evaluated dexmedetomidine 1µg/kg and clonidine 1µg/kg as adjuvant to 0.25% Ropivacaine in USG guided supraclavicular block. Onset of sensory block in dexmedetomidine group was 9.7+/-1.5 minutes, in clonidine group it was 12.9+/-1.4 minutes. Onset of motor block in dexmedetomidine group was 15.7+/-1.5 and in clonidine group it was 20.4+/-1.8 minutes. There was a faster onset for sensory and motor blockade in dexmedetomidine group.

In 2014, Rao et al.<sup>24</sup> conducted a prospective study to compare clonidine and dexmedetomidine as an additive in supraclavicular brachial plexus block where they noted that dexmedetomidine group had faster onset.

In most of the studies dexmedetomidine showed faster onset which was not comparable to our study. According to Haramritpal et al,<sup>23</sup> Khade Amit<sup>25</sup> (2013) the onset was found to be quicker in dexmedetomidine group.

In contrary to the above-mentioned studies, Rachana Gandhi et al<sup>21</sup> in 2012, the control group-C received injection bupivacaine (0.25%) 38 ml plus 2 ml normal saline versus dexmedetomidine 30 µg (2 ml) observed that in control group onset of motor block was faster. This was not comparable to our studies which showed slower onset of motor and sensory block with dexmedetomidine.

Singh et al<sup>16</sup> in 2010 compared the effects of clonidine added to bupivacaine alone in supraclavicular brachial plexus block in a randomized, controlled trial. 25 patients each were investigated using 40ml of 0.25% bupivacaine plus 0.150 mg of clonidine versus bupivacaine plus 1 ml NaCl 0.9%. It was found that clonidine to bupivacaine resulted in faster onset of sensory block.

Kohli et al<sup>18</sup> put 60 adult patients for upper limb surgeries under brachial block. Thirty patients received 1µg/kg clonidine versus another 30 received 2micro gram per kilo gram. Sensorimotor block was faster in the 2-micro gram per kilogram group.

Some studies failed to find any advantage of addition of Clonidine like- Singelyn et al,<sup>12</sup> Murphy et al, Hutschala et al,<sup>13</sup> BirbalBaj et al,<sup>19</sup> Kumkum Gupta et al who observed no faster block with clonidine added even in higher doses.

Studies may show different results for the block comparing dexmedetomidine and clonidine may be due to varying evaluation measures used. Can be due to varying pharmacokinetic effects resulting from using altered concentration of drugs or due to different block approaches like USG guided blocks, blind approach or nerve stimulator guided.

### Duration of Analgesia and Motor Block

Onset of pain requiring analgesia was taken as duration of sensory block and motor block recorded till complete return of the muscle power happened. This was in accordance with studies performed by Swami et al,<sup>17</sup> Esmoğlu et al,<sup>26</sup> Gandhi R et al<sup>21</sup> and Biswas et al.<sup>22</sup>

In Swami et al<sup>17</sup> the time for sensory block and motor block in clonidine group was 227+/- 48.36 and 292.67+/- 59.13 minutes respectively while it was 413.97+/-87.13 and 472.24+/-90.06 minutes in dexmedetomidine group. They found dexmedetomidine increased the sensory and motor block and also the time of analgesia. The time of block was almost twice compared to clonidine with enhanced quality of block. Jinjilet al.<sup>20</sup> 2015 comparing Dexmedetomidine and clonidine 1µg/kg each as additives to 0.25% Bupivacaine in USG guided Supraclavicular block showed time of sensory block was 690 minutes and 330 minutes respectively.

A RCT by Esmoğlu et al<sup>26</sup> assigned 60 patients to receive either 40 ml of 0.5% levobupivacaine with 1ml dexmedetomidine (100µg) of 0.5% levobupivacaine with 1ml of saline and found that sensory and motor onset time were significantly faster in study group compared to control group. Duration of sensory block (minutes) in Group L: 673.00+/- 73.77, in Group LD: 887 +/- 66.23. Duration of motor block (minutes) in Group L: 575.00 +/- 65.00, in Group LD: 773.00 +/- 67.62(85).

Gandhi R et al<sup>21</sup> assigned 70 patients to either 38ml of 0.25% bupivacaine with 30 µg of dexmedetomidine or plain 38ml of 0.25% bupivacaine only. They found block was longer in 30 µg of dexmedetomidine (660.2 ± 60.4 and 732 ± 48.9) compared to plain bupivacaine group (146.5 ± 36.4, 100.7 ± 48.3). We also found same results with increased duration of both sensory and motor blockade by using dexmedetomidine.

In 2014 Biswas et al<sup>22</sup> evaluated the effect of combining dexmedetomidine with levobupivacaine in a randomized double-blind prospective study. Sixty patients scheduled for elective forearm and hand surgery were divided into two groups. Brachial plexus block given via supraclavicular route with the help of nerve stimulator. In group L (n=30) 35cc of levobupivacaine with 1ml of isotonic saline and in group LD (n=30) 35cc of levobupivacaine with 1 ml of (100 microgram) of dexmedetomidine was given. They found that block was enhanced in group LD as compared to L (P<0.01).<sup>22</sup>

Few recent studies use USG to perform blocks whose results were also comparable to our study- Agarwal Set al<sup>28</sup> found dexmedetomidine as an additive to bupivacaine for brachial plexus block showed that duration of analgesia was prolonged in dexmedetomidine group. The duration or

sensory and motor blocks for study group were  $755.6 \pm 126.8$  and  $702.0 \pm 112.6$  min, respectively; but for the control group, the mean duration was  $234.8 \pm 47.9$  and  $208.0 \pm 22.7$  min, respectively.<sup>28</sup>

Ammar S et al<sup>27</sup> in their RCT on dexmedetomidine with bupivacaine in ultrasound guided infraclavicular brachial plexus block showed enhancement of sensory and motor blockade which was comparable to our study. They also showed that verbal rating scales for pain, postoperative opioid requirements were also less in dexmedetomidine group. Our study showed similar results.<sup>27</sup>

Our study also showed the duration of sensory block in Group C was  $9.7 \pm 1.6$  hours,  $13.3 \pm 1.9$  hours in Group D. Duration of motor blockade (hrs) was  $9.1 \pm 1.7$  hours in Group C,  $12.1 \pm 2.0$  hours in Group D. It was longer in dexmedetomidine group than clonidine. First rescue dose was required at  $10.5 \pm 1.7$  hrs in clonidine group and at  $15 \pm 2.2$  hrs in dexmedetomidine group. Results were statistically significant.

Popping et al<sup>15</sup> in 2009 did a meta-analysis of 20 studies (1,054 patients, 573 received clonidine) and found clonidine improved the duration of pain relief by 2 hours when added to intermediate or long acting local anaesthetics.

**Sedation Scores:** One of the strengths in our study was that we assessed sedation scores based on Ramsay scoring. Sedative premedication was avoided to abolish interference in scoring sedation. Significant variation in Sedation score was observed at 0 min and at 60 min. Highest sedation score was observed in clonidine group at 60 minutes. But our patients did not require any airway assistance. At other intervals no significant difference noted. Although sedation might be undesirable in certain situations like in high risk patients, mild sedation was desirable during that period as calm patient is 'ideal' for any regional.

Clonidine being a lipophilic drug, much of it gets absorbed in circulation after perineural application resulting in sedation.<sup>12</sup>  $\alpha_2$  - adrenergic agonists produce sedation by central action at the level of dorsal root neuron and by activation of  $\alpha_2$  - adrenergic receptors in locus ceruleus.<sup>22</sup>

Kohli et al<sup>18</sup> compared two different doses of clonidine 1 and 2  $\mu\text{g}/\text{kg}$  with local anaesthetic and concluded that there was no hemodynamic alteration with lower dose clonidine but 17% incidence of sedation with higher dose.

The quality of sedation produced by  $\alpha_2$  - agonists differs from the sedation produced by drugs like midazolam, propofol that act on gamma aminobutyric acid (GABA) receptors. Sedation produced by  $\alpha_2$  - agonists reflects decreased sympathetic nervous system activity, resulting in a calm patient who can be easily aroused to full consciousness.

We have done this study in ASA physical status 1 and 2 patients, we need to be extremely vigilant when we supplement opioids or benzodiazepines along with alpha 2 agonists for sedation in patients who are prone for respiratory compromise.

Adverse effects Studies showed reversible bradycardia <10% which is comparable to our study.<sup>15</sup>

Side effects like bradycardia observed in Esmoglu et al<sup>26</sup> and in Gandhi R et al<sup>21</sup> study. Subjects in clonidine group

had bradycardia, were as 3(10%) of subjects in dexmedetomidine group had Bradycardia, this probably due to the dosage of dexmedetomidine used which is 100  $\mu\text{g}$  in Esmoglu et al<sup>26</sup> study and 30 $\mu\text{g}$  in study by Gandhi R et al.<sup>21</sup>

In 1998, Singlynet al<sup>12</sup> observed that a minimum of 0.5mcg/kg clonidine needed to be given perineurally to prolong analgesia after brachial plexus block without producing adverse effects.

McCartney et al<sup>14</sup> took up 27 studies (1,385 patients). They concluded that clonidine proved to be a beneficial adjuvant when added to intermediate- acting local anaesthetics and side effects were limited to doses up to 150 mcg.

Usual complications due to supraclavicular block like pneumothorax, injury to vascular structures, horner's syndrome were not seen in our study. This may be because adjacent areas are well visualized with Ultrasound.

## Conclusion

Dexmedetomidine as an additive to .375% bupivacaine in a lower dose of 5mcg/kg proves to be superior to clonidine 5mcg/kg in ultrasound guided supraclavicular blocks. It considerably increases duration of block and also has lesser adverse effects at lower doses. But of worry is its unwelcomed long duration of motor block in the post-operative period. So, search for an adjuvant with selective prolonged analgesia without impairing motor function persists.

**Conflict of Interest:** None.

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