Research Article

The efficacy and safety of clonidine and dexmedetomidine as an adjuvant in supraclavicular brachial plexus block for elective upper limb surgery

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ABSTRACT

Background: Adjuvant play very important role in regional anesthesia and search for better adjuvant is still going on. **Objectives:** The objectives of this study are to find equipotent doses and to compare the efficacy of two α_2 agonists clonidine and dexmedetomidine as an adjuvant in supraclavicular block. **Materials and Methods:** A total of 90 patients of the American Society of Anaesthesiologists 1 and 11 of age 20-50 years undergoing elective upper limb surgeries under supraclavicular block divided into three groups: Group N: Received injection bupivacaine 0.5% 15 ml + injection. Lignocaine with adrenaline 2% 15 ml + normal saline 0.5 ml. Group D: 1 μg/kg dexmedetomidine. Group C: 1.5 μg/kg clonidine as studied drug in place of normal saline. Onset, duration of sensory and motor block, duration of analgesia, visual analog scale (VAS) score, hemodynamics, sedation, and other side-effects noted down. **Results:** Onset of sensory and motor block in Group D (8.13 ± 2.52 and 12.13 ± 2.90), Group C (7.97 ± 2.58 and 12.47 ± 2.89), and Group N (12.43 ± 2.57 and 17.97 ± 3.06) groups, respectively. Duration of sensory and motor block was 528.2 ± 105.27 and 464.17 ± 93.15 in Group D, 544.97 ± 113.51 and 476.57 ± 105.41 in Group C, and 292 ± 77.4 and 257 ± 75.63 in Group N, respectively. Duration of analgesia was 644.93 ± 118.45 in Group D and 646.93 ± 112.18 in Group C and 352.6 ± 84.39 in Group N. Both studied groups were comparable to each other in above parameters and are significantly better than Group N. VAS score in the post-operative period at 360 min was higher in Group N (5.12 ± 0.68) when compared to Group C (4.5 ± 0.73) and Group D (2.07 ± 0.94), respectively. **Conclusion:** Dexmedetomidine and clonidine as an adjuvant to supraclavicular block were found equipotent in the studied doses. However, post-operative VAS was found low in dexmedetomidine group.

KEY WORDS: Clonidine; Dexmedetomidine; Supraclavicular Block

INTRODUCTION

Regional anesthesia has revolutionized the world of anesthetics. Various regional techniques are popular among anesthesiologist due to ease of administration, excellent surgical anesthesia, satisfactory post-operative analgesia, and cost-effectiveness. Adjuvant plays very important role in regional anesthesia. They act synergistically with local anesthetics.[1-3] They improve quality of block, enhance post-operative analgesia, and increase the safety margin.

α_2 agonist popularly used as adjuvant to local anesthetics in various blocks. They are replacing opioids as it has its own side-effects.[4] α_2 agonist enhances both sensory and motor blockade of neuraxial and peripheral nerves.[1-3] The mechanism of action is hypothesized to be vasoconstriction around injection site, direct suppression of nerve impulse propogation, local release of enkephalin likes substances decreases in localized inflammatory mediators, and increase in anti-inflammatory cytokins.[5]

Our study was based on hypothesis that α_2 agonists as an adjuvant enhance the quality of block.[6-8] As there is a scarcity

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of studies comparing dexmedetomidine and clonidine in various doses, we compared dexmedetomidine 1 μg/kg and clonidine 1.5 μg/kg as adjuvants in supraclavicular brachial plexus block.

MATERIALS AND METHODS

This prospective randomized double-blind study was conducted in our institution, in the year 2016-2017. After the ethical committee approval 90 patients of age 20-50 year, either gender, American Society of Anaesthesiologists (ASA) Grade 1 or 2 undergoing upper limb elective orthopedic surgeries under supraclavicular brachial plexus block were enrolled in the study. After taking written and informed consent, they were divided randomly into three groups in 30 patients each.

- Group-N: Injection bupivacaine 0.5% plain 15 ml + injection lignocaine 2% with adrenaline 15 ml + normal saline 0.5 ml.
- Group-D: Injection bupivacaine 0.5% plain 15 ml + injection lignocaine 2% with adrenaline 15 ml + injection dexmedetomidine 1 μg/kg.
- Group-C: Injection bupivacaine 0.5% plain 15 ml + injection lignocaine 2% with adrenaline 15 ml + injection clonidine 1.5 μg/kg.

Exclusion criteria include patients who are unwilling for study, patient known hypersensitive to study medications, neurological and psychiatric illness, pregnancy, underlying significant systemic disorder, alcohol or drug abuse, patients with morbid obesity, diabetes, peripheral vascular disease or known allergies, incomplete or failed block.

The patients were randomly segregated into three study groups according to the list of random number table using a computer-generated randomization test or by another an esthetist not otherwise involved in this study.

On arrival in the operation room, baseline heart rate, blood pressure, and oxygen saturation were recorded. An intravenous line was secured in the unaffected limb. No premedication was administered.

Under all aseptic precautions, supraclavicular brachial plexus block was given in the patients by 22 gauge needle with the help of peripheral nerve locator. Sensory block will be assessed by the pinprick 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 no pinprick sensation (Grade 2) felt in all the dermatomes.

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 2 motor blockade.

Motor block was determined according to a modified bromage scale for upper extremities on a three-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.

Onset of Sensory Block

The time interval between administration of local anesthetic solution to loss of pin-prick sensation in all the dermatomes (Grade 2 in all the dermatomes).

Onset of Motor Block

The time interval between administration of local anesthetic solution to loss of movements, i.e. modified bromage scale (Grade 2).

Duration of Sensory Block

Time interval between loss of pin-prick sensation to the appearance of pin-prick sensation in any of the dermatome (Grade 1).

Duration of Motor Block

Time interval between loss of movements to the appearance of the movements (Grade 1).

Duration of Analgesia

Duration of analgesia was considered from the onset of sensory block till patient demands for rescue analgesia to the rating of visual analog scale (VAS) scale for pain 4.

Rescue analgesia was given by injection diclofenac. The block was considered incomplete when any of the segments supplied by median, radial, ulnar, and musculocutaneous nerve not have anesthesia even after 30 min of drug injection. When more than one nerve unaffected it was considered as a failed block and was not included in the study and same number of patients included further in the study.

All patients were monitored for vital parameters, pulse rate, blood pressure, and SpO_2 recorded at regular interval of 15 min intraoperatively. Sedation and other side-effects (nausea, vomiting, dryness of mouth and shivering) were also recorded during the course of study using Ramsay sedation

scale. Postoperatively, patients were assessed for pin-prick sensation, finger movement and demand for analgesia, every 30 min. VAS for pain was assessed at 360 min in all patients.

All recorded data wer statistically analyzed using SPSS version 10 and MS office Excel 2007. Data were expressed as mean±standard deviation and number (percentile) for all determination. Group "N" was used as a control group. Based on normality, parametric and nonparametric tests were declared statistically significant for $P < 0.05$ and statistically highly significant for $P < 0.001$.

RESULTS

The demographic variables such as age, gender, weight, and ASA grade were comparable in all these groups (Table 1).

The onset of sensory block was faster in Group D (8.13 ± 2.52) and Group C (7.97 ± 2.58) as correspond to Group N (12.43 ± 2.57) but it is not statistically found different when corresponding Group D with Group C ($P = 0.809$) (Table 2).

Duration of sensory block was 528.2 ± 105.27 in Group D and 599.97 ± 113.51 in Group C, respectively. Duration of sensory block is not statistically significant in Groups C and D however, when both values were compared to Group N (292 ± 77.48) and it is significantly prolonged ($P < 0.001$) (Table 2).

The onset of motor block in Group D (12.13 ± 2.90) and Group C (12.47 ± 2.89) was statistically faster than Group N (17.97 ± 3.06). But compared with each other, it was not statistically different ($P = 0.66$). Duration of motor block was 464.17 ± 43.15 in Group D, 476.57 ± 105.41 in Group C, and 257 ± 75.63 in Group N. It was statistically prolonged in Groups D and C as compared to Group N ($P < 0.001$), but not significantly different in two groups ($P = 0.631$) (Table 3).

Duration of analgesia was 644.93 ± 118.45 in Group D and 646.93 ± 112.18 in Group C as compared to 352.6 ± 84.39 in Group N. Again, duration of analgesia was statistically prolonged in Groups D and C as compared to Group N ($P < 0.001$). But did not differ from each other ($P = 0.9467$) (Table 2).

VAS score in the post-operative period at 360 min was higher in Group N (5.13 ± 0.68) as compared to Group C (4.5 ± 0.73) which in turn higher than Group D (2.07 ± 0.94). Thus, postoperatively patients of Group D had statistically significant pain relief as compared to Group C ($P < 0.001$), which in turn had statistically significant than Group N ($P < 0.001$) (Table 2).

Table 1: Demographic data

Characteristics	Group N (*n*=30)	Group D (*n*=30)	Group C (*n*=30)
Sex (male/female)	Male=24 Female=6	Male=22 Female=8	Male=17 Female=13
Age (in years)	36±12.69	31.9±11.15	36.37±10.84
Weight (in kg)	63.37±8.89	63.4±9.01	58.33±4.01
ASA grading			
Grade I	18	19	21
Grade II	12	11	09

ASA: American Society of Anesthesiologist, Data are expressed as mean±SD

Table 2: Characteristics of sensory block

Characteristics	Group N	Group D	Group C	*P* value		
				N/D	N/C	D/C
Onset of sensory block (min)	12.43±2.57	8.13±2.52	7.97±2.58	<0.001	<0.001	0.8089
Duration of sensory block (min)	292±77.48	528.2±105.27	544.97±113.51	<0.001	<0.001	0.5553
Duration of analgesia (min)	352.6±84.39	644.93±118.45	646.93±112.18	<0.001	<0.001	0.9467
VAS score (at 360 min)	5.13±0.68	2.07±0.94	4.5±0.73	<0.001	<0.001	<0.001

VAS: Visual analog scale (for pain), Data are given as mean±SD, $P<0.001$ is statistically highly significant

Table 3: Characteristics of motor block

Chacteristics	Group N	Group D	Group C	*P* value		
				N/D	N/C	D/C
Onset of motor block (min)	17.97±3.06	12.13±2.90	12.47±2.89	<0.001	<0.001	0.6509
Duration of motor block (min)	257±75.63	464.17±93.15	476.57±105.41	<0.001	<0.001	0.631

Data are given as mean±SD, $P<0.001$ is statistically highly significant

Systolic and diastolic blood pressure remained low in Group D and Group C as compared to Group N. No pharmacological treatment was needed (Table 4).

Pulse rate was lower in Group D and Group C as compared to Group N, which never fall below 60/min. If compare Group D with Group C, they did not show variations. Oxygen saturation was within normal range in all groups (Table 4 and Figure 1).

Ramsay sedation score of Group D was 3.37 ± 0.89 and Group C was 3.63 ± 0.85 as compared to sedation score of Group N (1.93 ± 0.52). Thus, patients of Groups D and C show statistically significant sedation ($P < 0.001$) (Table 5 and Figure 2). When comparing Groups D and C, sedation score did not found statistically different.

No side-effects (nausea, vomiting, shivering, and dry mouth) were reported during first 24 h in all studied patients.

DISCUSSION

Supraclavicular blocks are commonly used technique for upper limb surgeries. It is performed at the level of the brachial plexus trunks where almost entire sensory, motor and sympathetic innervations of upper extremities are carried in just three nerve structures (trunks) confined to a very small surface area. Typical features of this block include rapid onset, predictable, and dense anesthesia and high success rate. For prolonged surgeries, to avoid hassles of continuous brachial plexus block, various adjuvant are being used. α_2 agonists are safely used through various routes with promising effect as they prolong the duration of sensory and motor blockade, induced by local anesthetics irrespective of route of administration.[6-8] We had used clonidine and dexmedetomidine in a safe allowable doses to get maximum benefit.

Table 4: Hemodynamic parameters

Parameters	Group N (*n*=30)	Group D (*n*=30)	Group C (*n*=30)
SBP (mmHg)	117.79±8.21	112.42±14.84	112.91±7.45
DBP (mmHg)	78.01±3.31	73.21±3.61	73.37±3.77
PR (min)	82.36±3.85	80.16±5.98	79.74±5.9
SPO_2 (%)	99.63±0.59	99.37±0.77	99.42±0.74

Data are given as mean±SD, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PR: Pulse rate, SPO_2: Oxygen saturation

Keplinger et al. studied different doses of dexmedetomidine with local anesthetics for peripheral nerve block, and found significant dose-dependent increase in the mean duration of analgesia[9] and Singelyn et al. reported that a minimum dose of clonidine (0.5 µg/kg) added to mepivacaine prolongs the duration of anesthesia and analgesia in brachial plexus block. No added benefits were found with doses exceeding 1.5 µg/kg.[7] Therefore, we decided to use 1 µg/kg of dexmedetomidine and 1.5 µg/kg of clonidine in our study, so as to give us a better insight of efficacy of 2 drugs, safety profile and cost effectiveness of adjuvant.

Mechanism of Action of Clonidine

There have been four proposed mechanisms for the action of clonidine in peripheral nerve blocks. They are centrally mediated analgesia, $\alpha_2\beta$ adrenoceptor mediated vasoconstrictive effects, attenuation of inflammatory response, and direct action on peripheral nerve.[10] 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

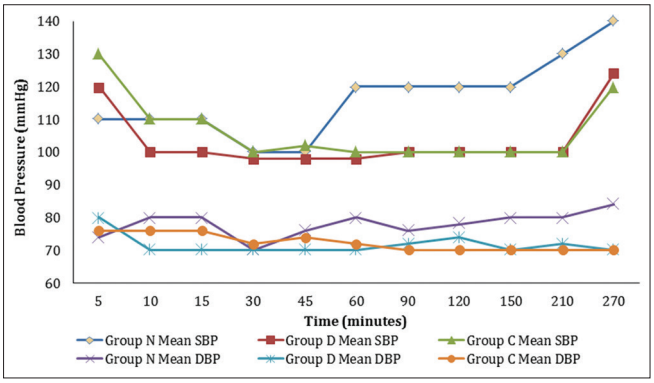

Figure 1: Comparison of mean systolic blood pressure and mean diastolic blood pressure in all the three groups (SBP: Systolic blood pressure, DBP: Diastolic blood pressure)

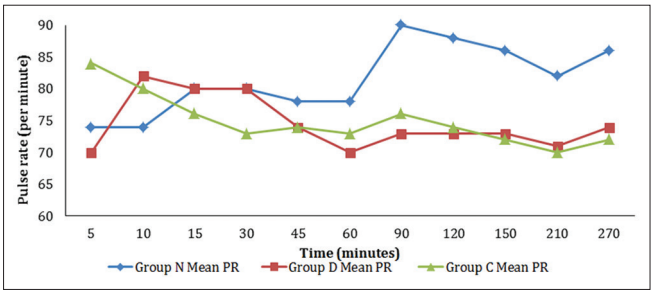

Figure 2: Comparison of mean pulse rate in all the three groups (PR: Pulse rate)

Table 5: Sedation score chart

Sedation score	Group N	Group D	Group C	*P* value		
				N/D	N/C	D/C
	1.93±0.52	3.37±0.89	3.63±0.85	<0.001	<0.001	0.252

Data are given as mean±SD, $P<0.001$ is statistically highly significant

by the Na/K pump during repetitive stimulation, increases the threshold for initiating the action potential causing slowing or blockage of conduction.[11]

Mechanism of Action of Dexmedetomidine

In a study, perineural 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 hyperpolarization-activated cation channel enhancer but not by an α_2 adrenoceptor antagonist. This shows that the analgesic effect of peripheral perineural 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] Dexmedetomidine inhibits CAPs in nerve fibers thereby causes analgesia, this action was not antagonized by α_2 adrenoceptor antagonists.

Dexmedetomidine is 8-10 times more selective toward α_2 adrenergic receptors and is 3.5 times more lipophilic than to clonidine[13] and 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[14-17]; thus, we were assuming dexmedetomidine would have better effect.

In our study, there was no statistically significant difference found in onset and duration of blocks in Groups D and C when compared with each other but was statistically significant in both groups, when compared to control group. This was supported by study of Esmaoglu et al., which stated that when dexmedetomidine added to levobupivacaine for axillary brachial plexus block, it shortens the onset time of both sensory and motor block, prolongs the duration of block and duration of post-operative analgesia.[16] 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.[15,16] The prolongation of motor block by Clonidine was supported by the study of Popping et al.[8] The other effects were supported by other similar studies.[18-21] Clonidine and local anesthetic agents have a synergistic action. Clonidine enhances both sensory and motor blockade of neuraxial and peripheral nerves after injection of local anesthetic solution.[1-3] This is thought to be due to blockage of conduction of A δ-fibers and C-fibers, increase in the potassium conductance in isolated neurons *in vitro* and intensification of conduction block achieved by local anesthetics.

VAS scores for pain were low in the Group D (2.07 ± 0.94) and Group C (4.5 ± 0.73) at 360 min both values were significantly lower than Group N (5.13 ± 0.63). Our result concurs with other similar studies.[18-20,22]

None of the patients in studied groups required sedation intraoperatively, and they were comfortable through the surgery with arousable sedative effects.[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 adrenoceptor in locus ceruleus.[23]

Our study showed stable hemodynamics throughout the surgery in both Groups D and C, supported by the study of Singh and Aggarwal[22] and Swami et al.;[24] however, Buttner et al. and Bernard and Macaire reported incidence of hypotension and bradycardia with the use of clonidine.[19,25]

We did not get any adverse effect in our study groups; most of the studies conducted using Clonidine in regional anesthesia did not report any adverse effects.[20]

CONCLUSION

Both clonidine and dexmedetomidine were found effective as an adjuvent to supraclavicular block. They cause early onset, and increased the duration of anesthesia and provide post-operative analgesia in the form of low VAS for pain. Patients remained hemodymics stable and sedated. However, when compared with each other, clonidine is as effective as dexmedetomidine in studied doses. The comparative dose of clonidine over dexmedetomidine needs to be explored in a large study population and different nerve blocks.

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