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ORIGINAL ARTICLE

THE EFFICACY OF CLONIDINE ADDED TO BUPIVACAINE AS COMPARED WITH BUPIVACAINE ALONE USED IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK FOR UPPER LIMB SURGERIES

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ABSTRACT: INTRODUCTION: Clonidine when added to local anesthetic solutions improved peripheral nerve blocks by reducing the onset time, improving the efficacy of the block during surgery and extending postoperative analgesia. **MATERIALS AND METHODS:** Sixty patients aged 18 to 60 years, scheduled for elective orthopedic operations in the upper limb, of ASA Grade I or II were included in the study. We conducted the study with 2 groups consisting of 30 patients each to compare the effects of Clonidine added to Bupivacaine with Bupivacaine alone in supraclavicular brachial plexus block. First group received 40 ml of Bupivacaine 0.25% plus 0.15mg (1ml) of Clonidine, second group had 40 ml of Bupivacaine 0.25% plus 1 ml 0.9% Saline respectively. The onset as well as duration of sensory and motor block along with monitoring of heart rate, NIBP, oxygen saturation were recorded. The level of sedation and side effects were also noted. **RESULTS:** In this study the addition of Clonidine to Bupivacaine resulted in faster onset (study group 15.2±1.44, control group 20.4±1.12, $p<0.001$) and longer duration of sensory block (study group 544±31.2, control group 302±34.4, $p=0.0363$) as well as analgesia (study group 561.2±30.96, control group 324.4±34.08, $p=0.0001$) without any adverse hemodynamic changes.

KEYWORDS: Brachial plexus block, bupivacaine, clonidine.

INTRODUCTION: Acute postoperative pain is the result of a complex physiological reaction to tissue injury. The dorsal horn of the spinal cord is the site of termination of primary afferents and there is complex interaction between such afferent fibers, intrinsic spinal neurons, descending pain modulating fibers, and various associated neurotransmitters such as serotonin, norepinephrine, acetylcholine, adenosine, and glutamate in the dorsal horn.[1] Local anesthetics administered as regional nerve blocks are utilized in providing postoperative pain relief in many surgical procedures by blocking signal traffic to the dorsal horn.

Certain drugs may be used as adjuvant to local anesthetics to lower doses of each agent and enhance analgesic efficacy while reducing the incidence of adverse reactions. Tramadol and fentanyl had been successfully used as adjuvants to local anesthetic in brachial plexus block.[2,3] The concurrent injection of Alpha-2 adrenergic agonist drugs has been suggested to improve the nerve block characteristic of local anesthetic solutions through either local vasoconstriction[4] and facilitation of C fiber blockade[5] or a spinal action caused by slow retrograde axonal transport or simple diffusion along the nerve.[6]

Clonidine is a selective Alpha-2 adrenergic agonist with some Alpha-1 agonist property. In clinical studies, the addition of clonidine to local anesthetic solutions improved peripheral nerve blocks by reducing the onset time, improving the efficacy of the block during surgery and extending postoperative analgesia.[7,8]

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Clonidine possibly enhances or amplifies the sodium channel blockade action of local anesthetics by opening up the potassium channels resulting in membrane hyperpolarization, a state in which the cell is unresponsive to excitatory input.[9]

A number of these studies have focused on the effect of clonidine as adjuvant to either lignocaine[8] or mepivacaine.[7] further; these studies were done using clonidine 150 mcg, a moderately high dose with its attendant risk of adverse drug reactions. We have also compared this moderately high dose of clonidine versus placebo as adjuvant to bupivacaine for brachial plexus block, by supraclavicular approach, for orthopedic procedures of moderate duration in our population.

MATERIAL AND METHODS: The study was conducted in Ramakrishna Mission Seva Pratisthan, Vivekananda Institute of Medical Sciences. Written informed consent was obtained from all patients and the study was approved by the Institutional Ethics Committee.

Sixty patients aged 18 to 60 years, scheduled for elective orthopedic operations in the upper limb, under supraclavicular brachial plexus block, were included in this study. They were of American Society of Anesthesiologists (ASA) Grade I or II physical status. The procedures were of moderate duration and included implant removal, both bone plating, fixation of lower third of humerus and olecranon fixation.

Patients receiving chronic analgesic therapy, those with severe cardiopulmonary disease, thyroid disorders, diabetes mellitus, central or peripheral neuropathies, history of allergy to local anesthetics, or other contraindications to regional anesthesia were excluded from the study.

The study was designed as a prospective, randomized, double-blind, placebo-controlled trial. Participants were allocated to two equal groups of 30 each using a computer generated random number list. Group A (study group) patients received 40 ml of 0.25% bupivacaine and 0.15mg (1ml) clonidine, while group B (control group) received 40 ml of 0.25% bupivacaine and 1 ml of 0.9% sodium chloride through a supraclavicular approach for brachial plexus block. The allocation sequence was generated by the author entrusted with statistical analysis.

The anesthesiologist administering the injections and observing the effects received serially numbered sealed envelopes indicating the A or B codes for the anesthetic mixture to be administered. The A and B syringes were loaded with drug by another author not involved in administering the injections and in further evaluation of the patients. All observations (hemodynamic variables, oxygen saturation, level of sedation, time required to achieve surgical block in the operation theater and the time to rescue analgesic in the post-anesthesia care unit) were also recorded in a blinded manner.

Once a patient was brought into the operation theatre, standard monitoring was set up, including noninvasive arterial blood pressure, heart rate, and pulse oximetry. An 18-gauge IV cannula was inserted in the forearm and an infusion started with lactated Ringer's solution. The surgical procedure was performed by using a standard arm tourniquet inflated to 70 mmHg higher than systolic blood pressure. Hemodynamic variables were measured 10 min before block placement and every 15 min thereafter till the end of surgery.

Nerve blocks were performed, with the aid of a nerve stimulator, by using a 22G short-beveled, insulated (Teflon-coated) 50 mm long stimulating needle. Stimulation frequency was set at 2 Hz, while the intensity of stimulating current was initially set to deliver 1 mA and gradually decreased to < 0.5 mA. Negative aspiration was performed while injecting the drug solution to avoid any intravascular placement.

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The onset of sensory and motor blocks on the operated limb were evaluated every 5 min after the completion of anaesthetic injection by one of the authors who were unaware of the drug combination administered. Sensory block was assessed by pinprick discrimination (with 22G hypodermic needle) and motor block was evaluated by asking the patient to move the forearm against resistance and to flex the forearm. A pinprick sensation on the contralateral arm was scored as 100 points. Patients were requested to compare pinpricks in the primary innervation areas of the respective nerves in the anesthetized arm with the contralateral arm as reference.

The scale ranged from 100 points (full sensation) to 0 points (no sensation). Brachial plexus block was considered successful by Vester-Andersen's criteria [10] when at least two out of four nerve territories (radial, ulnar, median, and musculo cutaneous) were effectively blocked. Onset of sensory block was defined as a reduction of sensibility to 30% or less while onset of motor block was defined as reduction of muscle power to grade 3 or less.

The time to surgical blockade was defined as the time from the end of anesthetic injection to loss of pinprick sensation along the distribution of the ulnar and radial nerves along with inability to circumrotate the thumb of the concerned limb. When surgical anesthesia was not achieved in a patient even after 30 min from the anesthetic injection, the case was considered as failed block and the operation was then performed under general anesthesia.

Following operation, all patients were observed in post-anesthesia care unit and received rescue analgesic as soon as they complained of any pain. This consisted of inj. tramadol 100 mg IV, repeated if necessary. Patients were given clear instruction to ask for a rescue analgesic as soon as they sensed discomfort caused by pain on the operated hand. The time from the end of anesthetic injection in the operated hand till the first request for postoperative rescue analgesic was recorded in each patient.

The primary outcome measure was duration of analgesia. This was estimated as the time interval from placement of the block till first injection of rescue analgesic. Secondary outcome measures were onset and duration of sensory and motor blockade and any suspected adverse drug reactions.

Noninvasive arterial blood pressure, heart rate and oxygen saturation monitoring was done throughout the procedure. The degree of sedation was evaluated by using the University of Michigan Sedation Scale (UMSS)[11] of 0 to 4[0=awake and alert; 1 = minimally sedated/sleepy, appropriate response to conversion and/or sound; 2 = moderately sedated, somnolent/sleepy, easily aroused with tactile stimulation and/or simple verbal command; 3 = deeply sedated/deep sleep, aroused only with significant stimulation and 4 = could not be aroused].

All patients were clinically assessed during discharge from the orthopedic ward and again after 3 weeks (at the first routine postoperative examination) for occurrence of any neurological complications.

All 30 patients in the two groups were considered for adverse event analysis. However, subjects who failed blocks were excluded from effectiveness assessment.

Duration of analgesia was taken as the outcome measure of interest for the purpose of sample size calculation. It was estimated that 23 subjects would be required per group in order to detect a difference of 30 min in this parameter between the two groups, with 90% power and 5% probability of Type 1 error. This calculation assumed a pooled standard deviation of 30 min for the duration of analgesia.

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Data are summarized as mean ± standard deviation or as percentages. Statistical analysis was performed by MS Excel 2010 software. Comparison of categorical variables between the two groups was by Chi-square test. Numerical variables were normally distributed and were compared by Student's unpaired' test. All analyses were two-tailed and $P < 0.05$ was considered statistically significant.

RESULTS: We recruited 30 subjects per group, more than the calculated sample size. The age, sex distribution, body weight and the duration of surgery in the two groups were found to be comparable (table1).

Table 2 shows onset and duration of sensory and motor blocks and post-operative requirement of rescue analgesia. It was found that the onsets of both sensory and motor blocks were significantly shorter in group A and durations of sensory block were also significantly greater in this group receiving clonidine. Requirement of rescue analgesia was delayed. The mean time from block placement to the first request for pain medication i.e. duration of analgesia was 561±30.96 min in the clonidine group but 324.4±34.08 min in the other group. This difference was highly significant ($p<0.001$) statistically as well as clinically.

Regarding time to onset of surgical block, this was also faster by 6 minutes in the clonidine adjuvant group A.

No statistically significant difference was observed in heart rate, blood pressure, and oxygen saturation between the two groups at any time.

The sedation score between clonidine and the control group was comparable throughout the study period. All the patients were alert (sedation score 1) in both the groups at all times of observation.

Adverse effect was observed in any of the groups.

	GROUP A	GROUP B
SEX (F/M)	12/18	14/16
AGE (years)	38.8±11.3878	38.6±11.975
HEIGHT (cms)	161.8±7.967	161±5.965
WEIGHT (kgs)	59.8±7.087	57±7.0466

TABLE 1. COMPARISON OF THE DEMOGRAPHIC DATA

	Onset of sensory block (min)	Onset of motor lock (min)	Duration of sensory block (min)	Duration of motor block (min)	Duration of analgesia (min)
Bupivacaine and clonidine (GROUP A)	15.2±1.44	17.2±1.44	544±31.2	464±39.2	561.2±30.96
Bupivacaine only (GROUP B)	20.4±1.12	22.4±1.12	302±34.4	260±32	324.4±34.08

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	p<0.001	p<.001	p=0.0363	p=0.2946	p=0.0001

Table 2. COMPARISON OF ONSET OF SENSORY AND MOTOR BLOCK, DURATION OF SENSORY, MOTOR, ANALGESIA BETWEEN GROUP A AND B

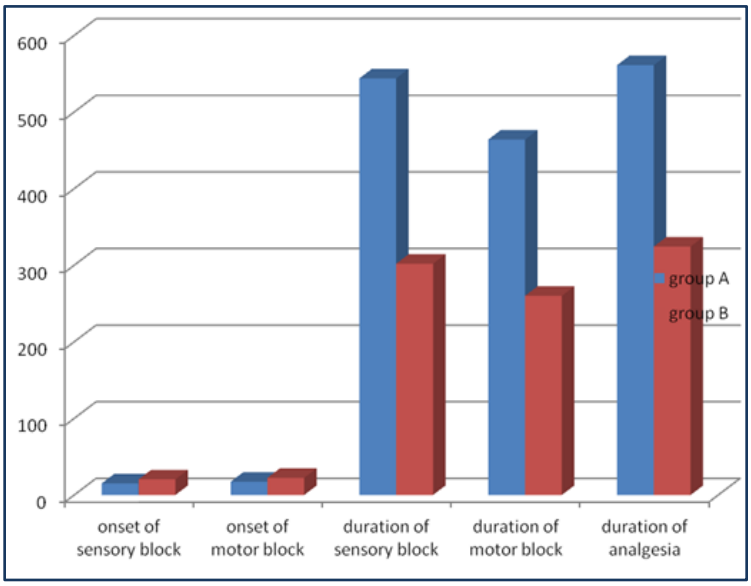

Fig.1 : Bar diagram representing table 2

diastolic BLOOD PRESSURE	(mm of Hg)										
	BASELINE	15min	30min	45min	60min	75min	90min	105min	120min	240min	480min
group A	80.06667	73.73333	76.43333	77.8	75.76667	79.6	78.2	78.8	77.5	78.5	76.7
groupB	78.93333	72.43333	74.93333	75.06667	74.23333	76.6	76.1	75.73333	76.23333	77.03333	74.86667

Table 3: Comparison of diastolic blood pressure between 2 groups

SYSTOLIC BLOOD PRESSURE (mm of Hg)											
	BASELINE	15min	30min	45min	60min	75min	90min	105min	120min	240min	480min
group A	130.5667	128.0333	129.2333	127.9	129.6	128.2	129.5667	130.7	130.3667	130.2333	129.9667
group B	130.5667	128.0333	129.2333	129.7667	132.8667	132.7333	129.5667	130.7	130.3667	130.2333	129.9667

Table 4: Comparison of systolic blood pressure between 2 groups

HEART RATE											
TIME	BASELINE	15	30	45	60	75	90	105	120	4 HRS	8HRS
group A	77.6	73.8	74.6	75.2	74.6	73.6	75.2	76.8	77.2	79	80.03333
group B	77.6	75.4	73	73.2	74.2	74.6	75.4	75.6	78	80.8	81.83333

Table 5: Comparison of heart rate between group A & B

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SPO2											
	BASELINE	15min	30min	45min	60min	75min	90min	105min	120min	240min	480min
group A	97.36667	98.86667	98.83333	98.86667	98.76667	98.96667	98.9	98.83333	98.9	97.4	97.6
group B	98.2	98.8	99	98.9	98.8	98.76667	98.8	99	98.8	98.2	98

Table 6: Comparison of saturation of oxygen between group A &B

DISCUSSION: The result of the present randomized controlled trial clearly suggests that clonidine, as adjuvant to 0.25% bupivacaine for supraclavicular brachial plexus block, prolongs the duration of analgesia as well as motor block. Onset times of blocks were also shown to be shortened though the study was not powered to measure these effects.

These findings are at variance with the study by Duma et al which showed no difference in analgesia after addition of clonidine 0.5 μg/kg to levobupivacaine in axillary block. [12] Probable explanation for this inconsistency may relate to inter-patient variations in the anatomy of the plexus sheath and difference in the spread of local anesthetics in the plexus sheath depending upon the block technique. More explanations may be forthcoming when the mechanism of adjuvant action of clonidine in this setting is elucidated.

Bernard and Macarie,[8] evaluating the effects of adding 30-300 μg clonidine to lignocaine for axillary brachial plexus anesthesia, reported that the addition hastened the onset of the block and improved the efficacy of surgical anesthesia. There are reported differences in the effects of administration of low-dose clonidine on time of onset and efficacy of nerve block, which may be explained by differences in the type of nerve block, exact mixture injected, and technique used to perform the block (single injection versus multiple injections). In fact, a multiple-injection technique was used, which is known to improve both onset time and quality of nerve block, [13] and this could have reduced the differences in onset time between the two groups.

In a dose-finding study evaluating the minimum effective dose of clonidine required to prolong duration of analgesia after axillary brachial plexus block, Singelyn et al[7] suggested that 0.5 μg/kg clonidine should be used. At this dose, significant prolongation of analgesia was achieved without undue sedation, hypotension, or bradycardia. It has been widely demonstrated in different studies that subcutaneous or intramuscular injection of clonidine is not as effective as perineural administration[14] suggesting that the local anesthetic-prolonging effect of clonidine is probably mediated locally at the neuron.[15]

This may also explain the variation in response in different types of peripheral nerve blocks, probably related to the rate and extent to which the injected anesthetic solutions penetrate into the nerve.[10] Even though injecting clonidine as the sole analgesic into the brachial plexus sheath does not provide clinically relevant analgesia,[16] it has been demonstrated to inhibit the action potential of A and C fibers in de-sheathed sciatic nerves.[9] Many authors favor the hypothesis that clonidine exerts its local anesthetic-prolonging effect directly on the nerve fiber, as a result of complex interaction between clonidine and axonal ion channels or receptors.[5,10,14] Peripheral antinociception induced by clonidine has also been related to 2-adrenoceptor-mediated local release of enkephalin-like substances.[17]

We selected a 150 µg dose of clonidine keeping in mind the hemodynamic adversities that might be produced. It was found that this dose provided satisfactory prolongation of the duration of analgesia without producing significant hemodynamic compromise in the patients. But we need a dose finding study to come up with the ideal dose of clonidine as adjuvant to 0.25% bupivacaine for supraclavicular brachial plexus block.

In conclusion, clonidine added to bupivacaine is an attractive option for improving the quality and duration of supraclaicular brachial plexus block in upper limb surgeries.

REFERENCES:

1. Yaksh TL, Hua XY, Kalcheva I, Nozaki-Taguchi N, Marsala M. The spinal biology in humans and animals of pain states generated by persistent small afferent input. ProcNatlAcadSci USA 1999; 96: 7680-6.
2. Kaabachi O, Ouezini R, Koubaa W, Ghrab B, Zargouni A, Ben Abdelaziz A. Tramadol as an adjuvant to lidocaine for axillary brachial plexus block. Anesth Analg 2007; 23: 187-9.
3. Karakaya D, Bóyókgφz F, Bariώ S, Góldoπuώ F, Tór A. Addition of fentanyl to bupivacaine prolongs anesthesia and analgesia in axillary brachial plexus block. Reg Anesth Pain Med 2001; 26: 434-8.
4. Gaumann DM, Forster A, Griessen M, Habre W, Poinsot O, Della Santa D. Comparison between clonidine and epinephrine admixture to lidocaine in brachial plexus block. Anesth Analg 1992; 75: 69-74.
5. Gaumann DM, Brunet PC, Jirounek P. Clonidine enhances the effects of lidocaine on C-fiber action potential. Anesth Analg 1992; 74: 719-25.
6. Khasar SG, Green PG, Chou B, Levine JD. Peripheral nociceptive effects of alpha 2-adrenergic receptor agonists in the rat. Neuroscience 1995; 66: 427-32.
7. Singelyn FJ, Gouverneur JM, Robert A. A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Anesth Analg 1996; 83: 1046-50.
8. Bernard JM, Macarie P. Dose-range effects of clonidine added to lidocaine for brachial plexus block. Anesthesiology 1997; 87: 277-84.
9. Butterworth JF 5th, Strichartz GR. The alpha 2-adrenergic agonists clonidine and guanfacine produce tonic and phasic block of conduction in rat sciatic nerve fibers. Anesth Analg 1993; 76: 295-301.
10. Vester-Andersen T, Eriksen C, Christiansen C. Perivascular axillary block III: Blockade following 40 ml of 0.5%, 1% or 1.5% mepivacaine with adrenaline. ActaAnaesthesiolScand 1984; 28: 95-8.
11. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N. Depth of sedation in children undergoing computed tomography: Validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth 2002; 88: 241-5.
12. DumA A, Urbanek B, Sitzwohl C, Kreiger A, Zimpfer M, Kapral S. Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: a randomised controlled study. Br J Anaesth 2005; 94: 112-6.

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13. Casati A, Fanelli G, Beccaria P, Cappelleri G, Berti M, Aldegheri G, et al. The effects of the single or multiple injection technique on the onset time of femoral nerve blocks with 0.75% ropivacaine. Anesth Analg 2000; 91: 181-4.
14. Eisenach JC, De Kock M, Klimscha W. Alpha (2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology 1996; 85: 655-74.
15. Hutschala D, Mascher H, Schmetterer L, Klimscha W, Fleck T, Eichler HG, et al. Clonidine added to bupivacaine enhances and prolongs analgesia after brachial plexus block via a local mechanism in healthy volunteers. Eur J Anaesthesiol 2004: 21: 198-204.
16. Sia S, Lepri A. Clonidine administered as an axillary block does not affect postoperative pain when given as the sole analgesic. Anesth Analg 1999; 88: 1109-12.
17. Nakamura M, Ferreira SH. Peripheral analgesic action of clonidine: Mediation by release of endogenous enkephalin-like substances. Eur J Pharmacol 1988; 146: 223-8.

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