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Effect of Addition of Clonidine on the Onset and Duration of Action of Bupivacaine in Brachial Plexus Block.

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Abstract:Introduction*; In this study,we evaluated the effect of Clonidine with Bupivacaine on the onset and duration of analgesia on Supraclavicular brachial plexus block.****Methodology****: After taking institutional ethical committee's approval and getting informed consent from the patients, 60 patients were randomly divided into two groups Group A and Group B. Group A patients received 0.5% Bupivacaine 2mg per kg bodyweight,Group B received 0.5% Bupivacaine 2mg per kg bodyweight plus Clonidine 2µg per kg bodyweight .* ***Results:*** *In our study the mean duration of analgesia in Group B is 8.566 mints and in Group A it is 7.266 mints.****Conclusion****: We conclude from our study that addition of Clonidine prolonged the duration of analgesia in Supraclavicular brachial plexus block.*

Keywords*: Supraclavicular brachial plexus, analgesia, Clonidine,*

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I. Introduction:

Pain is one of man's most compelling experience. It is an unpleasant sensation which only the individual himself can appreciate and as such incapable of a satisfactory definition.

Herrington (1906) in his classic work on central Nervous System has defined pain as "The Psychical adjunct to an imperative protective reflex" and the concept certainly draws attention to the protective aspects of pain in preventing body injury by noxious stimuli. The effects of postoperative pain are largely psychological, causing distress and anxiety and can be associated with less serious autonomic disturbances such as sweating and nausea. Therefore the most obvious motive for relieving postoperative pain is the humanitarian one. Good postoperative pain relief can reduce the metabolic response to trauma and thus may prevent or postpone postoperative negative nitrogen balance. Another advantage is that the patient has better mobility with immediate benefits of reduced incidence of chest infections and deep vein thrombosis.

There is definite scope for improvement in this area. Introduction of newer narcotics, patient controlled analgesia using sophisticated equipment, using opioids in regional block and spinal opiate analgesia are some steps in this direction.

Brachial plexus block is a valuable adjunct to general anesthesia for surgery of the upper limb or a suitable alternative to general anesthesia in high risk patients. The techniques of peripheral nerve blockade were developed early in the history of anesthesia and are now well-accepted components of comprehensive anesthetic care. Its role has expanded from the operative site into the area of postoperative and chronic pain management. With appropriate selection and sedation, these techniques can be used in all age groups. Skillfull application of peripheral neural blockade broadens theanesthesiologist's range of options in providing optimal anesthetic care.

Even though so many approaches and techniques came into practice, still the supraclavicular brachial plexus block is the standard and acceptable technique for arm and forearm surgeries. The confidence and co-operation of the patient are required for effective successful block.

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 an adjuvant to local anesthetics to lower the doses of each agent and enhances analgesic efficacy while reducing the incidence of adverse reactions. Tramadol and Fentanyl have been successfully used as an adjuvant to local anesthetics, in brachial plexus block[1-2].

The existence of α type receptors, which take part in the transmission of nociceptive stimuli at the spinal level, emphasizes a possible direct action of α adrenergic agonists on neuronal tissue[3].

The concurrent injection of α_2 adrenergic agonist drugs has been suggested to improve the nerve block characteristics of local anesthetic solutions through either local vasoconstriction [4] and facilitation of C fiber

blockade [5] or spinal action caused by slow retrograde axonal transport or simple diffusion along the nerve. Clonidine is a selective α_2-adrenergic agonist with some α_1 agonist properties. [6.]

Clonidine is a α_2 agonist used in subarachnoid [7,] epidural[8], brachial plexus [9,] blocks. It exerts its action in the peripheral nervous system by decreasing the secretion of Noradrenaline and inhibiting depolarization of nociceptive neurons in primary afferent nerve endings by binding to α receptors, subtypes A and C. In the central nervous system, it inhibits neuronal transmission in different areas of the brain, such as: the nucleus of the solitary tract and lateral reticular nucleus of the ventrolateral spinal cord. Studies suggest that Clonidine reduces the release of glutamate and noradrenaline and inhibits the opening of potassium channels. It also has synergistic effects with local anesthetics, blocking conduction in A-delta and C fibers. Indirectly, it can reduce the absorption of local anesthetics[10,]

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 [11.] The effect of Clonidine is dose related between 0.1 and 0.5µg/kg [11]. Clonidine possibly enhances or amplifies the sodium channels blockade action of local anesthetics by opening up the potassium channels resulting in membrane hyper polarization, a state in which the cell is unresponsive to excitatory input [12.]

Aim Of The Study:

The purpose of this dissertation is to study and compare the effectiveness of
Clonidine in 0.5% Bupivacaine over 0.5% Bupivacaine alone in supraclavicular brachial plexus block in terms of

1. Onset of analgesia
2. Duration of analgesia.

II. Materials And Methods:

This randomized prospective study was conducted at NRI General Hospital, in 60 patients presenting for upper limb surgery with a proposed average duration of two to three hours, after obtaining approval from the hospital ethics committee. A thorough preoperative evaluation by Anesthesiologist of all the patients was ensured. For each patient in both groups, the following information was acquired and tabulated. Age, sex, associated medical problems etc.

These 60 patients were divided into two groups . Each group comprised of thirty patients.
Group-1: 0.5% Bupivacaine 2 milligrams per kg body weight.
Group-11: 0.5% Bupivacaine 2 milligrams per kg body weight plus Clonidine 2µg per kg body weight.

Inclusion Criteria:

Sixty patients between

1. The age group of 20-60 years
2. ASA class-I and class-II
3. Scheduled to undergo upper limb surgery with duration of surgery lasting 120-180 minutes.

Exclusion Criteria:

Patients with

1. Neurological disorders
2. Anemia
3. Hypertension and any cardiac and respiratory disorders.

Informed consent was obtained from every patient. In both groups all patients were explained and reassured about the procedure. All patients were pre-medicated with tab. Alprazolam 0.5 mg the night before surgery.An assessment was made for onset of analgesia and duration of analgesia.

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Intra Operative Protocol

.In the operation theatre, intravenous access was secured with 18G cannula on the opposite limb and IV fluid was started. All the basic monitoring devices like SPO_2, ECG, NIBP were attached and baseline parameters were recorded.

Supraclavicular block was performed using nerve stimulation technique in the supine position with head turned $45^0$to the opposite side and arm placed by the side of chest. Needle insertion site was prepared with antiseptic solution. About 1-1.5 cm above the midclavicular point subclavian artery pulsations were felt, 50mm long insulated needle was inserted in caudal, backward and medial direction. When muscle wera seen at stimulating current between 0.2 Ma AND 0.5Ma AT 2Hz frequency with pulse width of 0.1ms,drugs were injected with intermittent negative aspiration

An assessment was made for onset of analgesia and duration of analgesia,

1. Onset of analgesia: It was taken as the period after injection of the analgesic solution to the absence of pin prick sensation at the surgical site.

2. Duration of analgesia: It was taken as the period from the time of loss of pinprick sensation to the first appearance of pin prick sensation at the surgical site.These observations were made by another anesthesiologist who did not know what drug was administered to the patient.

Statistical Analysis:

We have studied 60 patients for difference in the onset and duration of action using standard descriptive statistics.

The following descriptive statistics were used to present the data

1. Tabulation
2. Graphical representation
3. Measures of central tendency

Statistical analysis to compare the variables like age, sex, onset and duration of action between the two groups was made by STUDENT 't' TEST

Student T Test was used to find if a significant difference existed between the twoGroups

'P' Value of < 0.05 was accepted as indicative of statistical significance and a 'p' value of > 0.05 was considered as non significant.

'P' value of < 0.01 and < 0.001 were considered as highly and very highly significant respectively.

III. Results:

Demographic Data: 60 patients were enrolled into the study, 30 in each, Group-A plain Bupivacaine, Group-B Bupivacaine plus Clonidine.

The pre operative demographic data (sex and age) were shown in the table 1 and 2

SEX distribution between group A and group B for 60 patient

Table 1: Gender distribution

	GROUP A	GROUP B
MALE	20	22
FEMALE	10	8

BUPIVACAINE WITH CLONIDINE- There are 30 patients in group B, out of which 22 patients are male and 8 patients are female.

PLAIN BUPIVACAINE- There are 30 patients in group A, out of which 20 are male and 10 are female.

Table 2 AGE distribution between group A and group B for 60 patients

	Group A	**Group B**
MEAN AGE + SD	37.43+15.03	38.46+13.52

P VALUE 0.2

Onset of Analgesia

The onset times of the two groups are shown in table 3 and table 4

Table 3ONSET times of the 30 patients in group A are given in table 3

Onset of analgesia in minutes	No of cases
0-10	19
10-20	10
20-30	1
30- 40	0
40-50	0
50-60	0

Onset of Analgesia

Table .4 ONSET times of 30 patients in group B are given in table 4

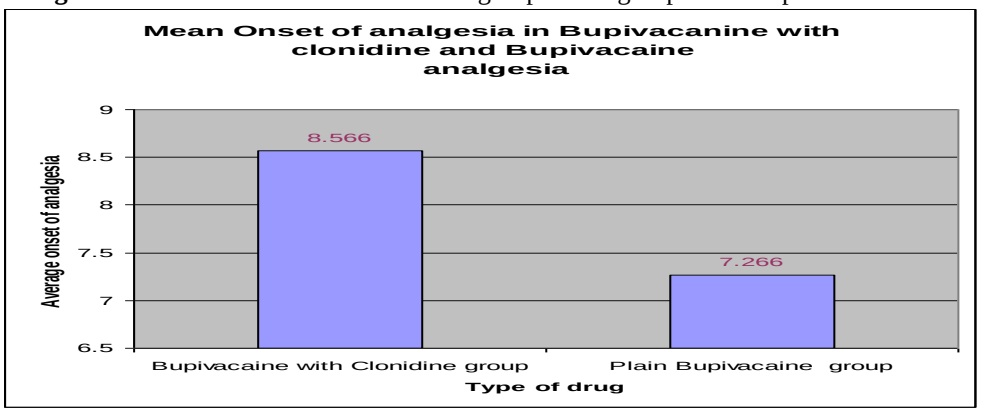
Onset of analgesia in minutes	No of cases
0-10	22
10-20	8
20-30	0
30- 40	0
40-50	0
50-60	0

0nset of Analgesia in Group B

Table 5 Mean onset time plus standard deviation of the two groups are shown in table 5

	GROUP A	GROUP B
ONSET TIME(MIN) + SD	7.266+2.36	8.566+4.07

Figure 1 MEAN ONSET TIME between group A and group B for 60 patients as shown



GROUP-A – The mean onset of action is 7.266± hours.
GROUP-B –The mean onset of action is 8.566±4.07 hours
The p value is 0.47 which indicates that there is no statistically difference between the mean onset of actions between the two groups.
Duration
The mean duration of action of two groups are shown in table 6 and table 7

Table – 6 The duration of action of the 30 patients in group A are given in table 6

Group A

Duration of analgesia	No of cases
4-6hrs	**0**
6-8hrs	**22**
8-10 hrs	**7**
10-12 hrs	**1**
12-14 hrs	**0**
14-16 hrs	**0**

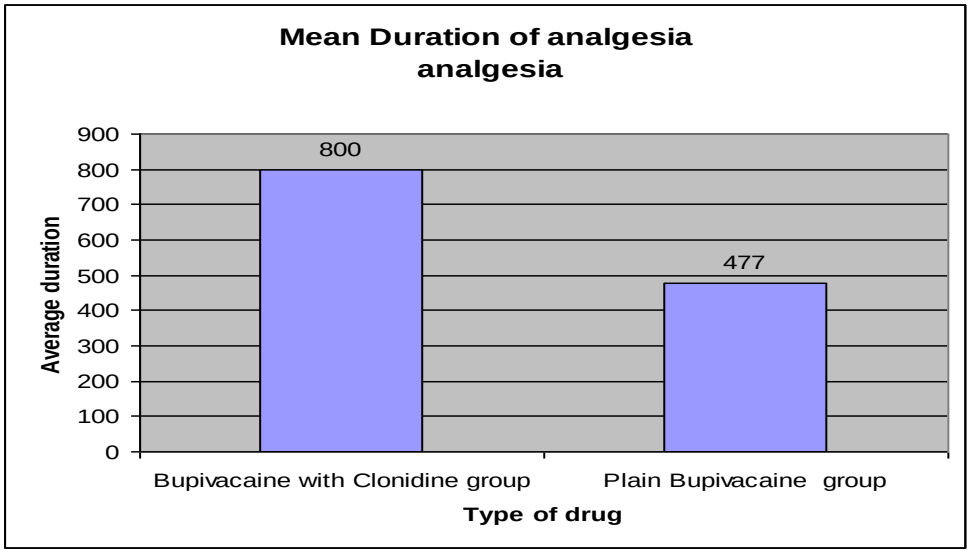
Table – 7 The duration of action of the 30 patients in group B are given in table 7

Duration of analgesia	No of cases
4-6hrs	**0**
6-8hrs	**2**
8-10hrs	**4**
10-12hrs	**4**
12-14hrs	**6**
14-16hrs	**12**

Table 8 The mean duration of action plus standard deviation of two groups are shown in table 8

	GROUP A	**GROUP B**
DURATION(HRS) ±SD	477+81.25	800+163.4

Figure 2 The mean duration of action of two groups is shown in bar diagram.



P VALUE- 0.001

GROUP A –mean duration of action is 477 ± 81.25 minutes

GROUP B – mean duration of action is 800 ± 163.4 minutes

The P value is 0.001 which indicates a highly significant difference in the duration between the two groups.

The summary of the results are that demographically both the groups are comparable as there is no significant difference between the two groups. Regarding the mean onset time there is a statistically no significant difference between the two groups($p > 0.05$). So addition of clonidine to bupivacaine, in terms of duration of action, is concerned there is a statistically significant difference between the two groups ($p < 0.001$). Addition of clonidine did not have any effect on the mean onset of action between the two group **DISCUSSION:**

Supraclavicular blocks are performed at the level of the brachial plexus trunks. Here almost the entire sensory, motor and sympathetic innervations of the upper extremity are carried in just three nerve structures (trunks), confined to a very small surface area. Consequently, typical features of this block include rapid onset, predictable and dense anesthesia along with its high success rate.

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, without affecting the onset[13]. This is thought to be due to blockade of conduction in A-delta and C fibers, increase in the potassium conductance in isolated neurons best seen in vitro and intensification of conduction block achieved by local anesthetics .

Clonidine, an imidazole compound, has long been used as an anti-hypertensive agent that produces reductions in blood pressure and heart rate. These effects result from central and peripheral $alpha_2$ agonist activity. There is a reduction in sympathetic nervous system outflow which involves the endogenous opioid system[14] and an impairment of peripheral adrenergic neurotransmission by activation of inhibitory presynaptic alpha2 receptors, which leads to increased parasympathetic nervous system activity. Clonidine has also been shown to have alpha1 agonist properties, [15]. So, its mechanism of action and effects are complex.

The results of our study showed no significant difference in onset of motor or sensory block when plain local anesthetic was compared with anesthetic plus clonidine in supraclavicular brachial plexus. These findings are in accordance with those of previous trials[16,17].

Bernard and Macarie, [11], 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 anesthesiaWith regard to prolongation of block, the results of our study showed that there is a significant prolongation of duration of analgesia when clonidine is added as a adjuvant.

There are two main theories on how clonidine may prolong sensory anesthesia [18]. One of these suggests that clonidine may produce local vasoconstriction, resulting in a delayed absorption of local anesthetic and block prolongation [19,20].The second is that clonidine may directly bind to alpha$_2$-adrenergic receptors to modify neuronal excitability rather than acting centrally on the locus coeruleus. Our data seem to confirm the local effect of clonidine because of the higher incidence and longer duration of motor blocks observed in patients who received the drug, as suggested in a previous report [21].

Clonidine has been shown to be of benefit for use in central neuraxial blocks and other regional blocks by increasing the duration and intensity of pain relief and also by decreasing the systemic and local inflammatory stress response .

In this study we combined Clonidine along with a local anesthetic to study how the onset and duration are affected.

We found a significant difference in the duration of analgesia between the two groups. We found that there was no significant difference in the onset of sensory block.

These findings indicate prolongation of analgesia with the use of Clonidine. The prolongation of analgesia observed is consistent with other trials performed at the brachial plexus, [22], popliteal block and in another study in children undergoing a variety of blocks, which demonstrated that the addition of Clonidine to Bupivacaine and Ropivacaine can extend sensory block by a few hours and increase the incidence of motor block ¨

Thus it is evident that the recovery of sensation was prolonged in Clonidine group. Our results concur with other similar studies[23,24]. Thus we favour the hypothesis that Clonidine exerts an effect directly on the nerve firer as a result complex interaction between Clonidine and axonal inotropic, metabolic or structural proteins (= receptors),which was shown in different laboratory studies.

We also found an enhancement of perioperative analgesia and prolongation of recovery of sensation in Clonidine group ,well beyond the pharmacological effect of either Clonidne or Bupivacaine. Direct modulation of the activity of sensory nerve fibres could conceivably explain the difference between the two groups in our study. Alternatively this could have been a result of overall better quality of anesthesia at all times of surgery .Regardless of the mechanism, Clonidine was found to have a valuable advantage in the field of peripheral nerve blocks when added to Bupivacaine.

In conclusion we have shown that the addition of Clonidine to Bupivacaine produced a longer duration of analgesia than plain Bupivacaine in the brachial plexus block. Therefore Clonidine is an attractive option to prolong analgesia in the postoperative period in patients undergoing upper limb surgeries under supraclavicular brachial plexus block

IV. Conclusion

In this study

1.Addition of Clonidine two micrograms per kg produced prolonged duration of action of 0.5% Bupivacaine in supraclavicular brachial plexus block.

2.Clonidine did not have any effect on the onset of action of 0.5% Bupivacaine in supraclavicular brachial plexus block

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