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Clonidine as an adjuvant to 0.25% bupivacaine and 0.25% levobupivacaine in supraclavicular brachial plexus block: Post-operative hemodynamics

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Abstract
Local anaesthetics are drugs that produce reversible conduction blockade of impulse along central and peripheral nerve pathways after regional anaesthesia. With progressive increases in concentrations of local anaesthetics, the transmission of autonomic, somatic sensory and somatic motor impulses are interrupted, producing autonomic nervous system blockade, sensory anaesthesia, and skeletal muscle paralysis in the area innervated by the affected nerve. A prospective, randomized, double blinded comparative clinical study was conducted in 80 patients of either sex requiring elective upper limb surgeries after obtaining an informed written consent. Statistical analysis of post-operative hemodynamic parameters included, Heart rate (HR), systolic (SBP) and diastolic blood pressures (DBP), Mean arterial pressures (MAP) and peripheral oxygen saturation (SpO2).

Keywords: Bupivacaine, clonidine, supraclavicular brachial plexus block

Introduction

Anatomical knowledge of brachial plexus and its cutaneous and muscular distribution is essential for the effective use of brachial plexus block for upper limb surgeries. Familiarity with the vascular, muscular and fascial relationships of the plexus is also essential for the mastery of various percutaneous techniques for performing the brachial plexus block [1].

Regional anesthestic techniques for surgeries of upper extremity require a thorough knowledge of brachial plexus anatomy to facilitate the technical aspects of block placement and optimize the patient-specific block selection. The brachial plexus is defined as that network of nerves supplying the upper extremity and formed by the union of the ventral primary rami of cervical spinal nerves 5 through 8 (C5-C8), including a greater part of the first thoracic nerve (T1). Variable contributions may also come from the fourth cervical (C4) and second thoracic (T2) nerves. Variable contributions may also come from the fourth cervical (C4) and second thoracic (T2) nerves [2].

Local anaesthetics are drugs that produce reversible conduction blockade of impulse along central and peripheral nerve pathways after regional anaesthesia. With progressive increases in concentrations of local anaesthetics the transmission of autonomic, somatic sensory and somatic motor impulses are interrupted, producing autonomic nervous system blockade, sensory anaesthesia, and skeletal muscle paralysis in the area innervated by the affected nerve. Removal of the local anaesthetic is followed by spontaneous and complete return of nerve conductions, with no evidence of structural damage to nerve fibres. Local anaesthetics have similar configuration. They have one aromatic lipophilic part (Benzene ring) and one hydrophilic part (quaternary ring) connected by an intermediate ring either ester (-COO-) or an amide (-NHCO-) [3].

The primary cardiac electrophysiologic effect of local anaesthetic is a decrease in the maximum rate of depolarization in the purkinje fibres and ventricular muscle.

This is due to a decrease in the availability of sodium channels. Action potential duration and the effective refractory period is also decreased. The depression of rapid phase of depolarization (V-max) in purkinge fibres and ventricular muscle by Bupivacaine is far greater compared to Lignocaine. Also the rate of recovery of block is slower with Bupivacaine. Therefore there is incomplete restoration of V-max between action potential particularly at higher heart rates [4]. Therefore, Bupivacaine is highly arrythmogenic.

The cardiac contractility is reduced, this is by blocking the calcium transport. Low concentration of Bupivacaine produces vasoconstriction while higher doses cause vasodilatation [5].

Methodology

A prospective, randomized, double blinded comparative clinical study was conducted in 80 patients of either sex requiring elective upper limb surgeries.

Patients enrolled in the study were randomly allocated to 2 groups of 40 each by random number table method, the study drugs were prepared outside the operating room by another anesthesiologist not involved in the study, namely:

Study group BC- received 30ml of 0.25% Bupivacaine plus 1µg/kg Clonidine

Study group LC- received 30ml of 0.25% Levobupivacaine plus 1µg/kg Clonidine

Inclusion criteria

- Patients aged between 18 to 60 years of either sex.
- ASA physical status I-II
- Elective upper limb surgeries

Exclusion criteria

- Patient refusal for procedure
- Any bleeding disorder or patient on anticoagulants
- Neurological deficits involving brachial plexus
- Patients with allergy to local anaesthetic drugs
- Local infection at the injection site
- Patients weighing less than 35kgs
- Body mass index >35

After Pre anesthetic evaluation and obtaining informed written consent, patients were kept nill per orally for eight hours and premedicated with Tab. Ranitidine 150mg and Tab. Alprazolam 0.5mg orally on the night before surgery. In the operating theatre, 18G intravenous cannula was secured and Ringer's lactate infusion was started. Standard monitoring devices ECG, Non invasive blood pressure, pulse oxymeter were attached and continuously monitored. Supraclavicular brachial plexus block was performed using peripheral nerve stimulator, study drugs were injected after obtaining motor response with the nerve stimulator for less than 0.5mA. after the surgery, patients were shifted to post operative area and the hemodynamic parameters such as Heart rate (HR), systolic (SBP) and diastolic blood pressures(DBP), Mean arterial pressures (MAP) and peripheral oxygen saturation (SpO2). were measured at different intervals for 24 hours. For descriptive statistics of continuous data Independent 't' test was used to compare blood pressure and heart rate between the two study groups. Anova test was used to compare individual pairs of groups.

Results

Statistical analysis of post operative hemodynamic parameters included, Heart rate (HR), systolic (SBP) and diastolic blood pressures (DBP), Mean arterial pressures (MAP) and peripheral oxygen saturation (SpO2).

The parameters were comparable and statistically insignificant in both the groups

Table 1: Comparison of Postoperative HR (bpm) in two groups of patients studied

Post-op Heart rate (bpm)	Group BC	Group LC	P value
0min	74.40±5.57	75.25±5.30	0.486
15min	76.20±5.22	76.40±5.61	0.869
30min	74.85±5.04	77.75±6.81	0.033*
45min	73.40±4.01	77.80±5.00	<0.001**
1hrs	70.25±4.90	75.90±3.68	<0.001**
2hrs	67.300±4.29	75.35±2.95	<0.001**
3hrs	64.85±3.23	74.65±3.49	<0.001**
4hrs	63.45±2.64	72.75±3.41	<0.001**
5hrs	63.25±3.26	72.50±4.41	<0.001**
6hrs	64.45±5.09	73.30±3.22	<0.001**
7hrs	67.25±5.33	74.65±1.78	<0.001**
8hrs	71.95±4.80	74.35±2.75	0.008**
12hrs	68.70±5.33	72.85±2.48	<0.001**
24hrs	73.20±4.27	73.45±3.00	0.763

Table 2: Comparison of SBP (mm Hg) in two groups of patients studied

Post-op SBP (mm Hg)	Group BC	Group LC	P value
0min	129.10±12.30	128.55±8.99	0.820
15min	129.20±10.89	129.25±8.15	0.982
30min	128.05±12.43	128.75±8.80	0.772
45min	126.10±11.29	127.20±8.81	0.628
1hrs	124.10±11.83	126.90±10.03	0.257
2hrs	119.85±7.80	123.65±9.19	0.050+
3hrs	116.65±9.29	122.50±8.54	0.004**
4hrs	116.50±7.88	120.25±7.32	0.030**
5hrs	115.55±6.20	121.75±7.51	<0.001**
6hrs	116.95±5.73	120.65±7.88	0.019*
7hrs	119.50±6.67	123.85±5.42	0.002**
8hrs	122.15±7.04	123.95±5.46	0.205
12hrs	123.60±8.70	123.65±5.92	0.976
24hrs	124.80±9.45	123.05±7.25	0.356

Table 3: Comparison of DBP (mm Hg) in two groups of patients studied

Post-op DBP (mm Hg)	Group BC	Group LC	P value
0min	83.20±4.81	81.40±5.25	0.114
15min	83.25±6.07	81.25±4.04	0.087+
30min	82.45±4.61	81.00±5.78	0.219
45min	80.80±2.71	80.70±5.14	0.914
1hrs	79.75±2.57	81.20±3.94	0.055+
2hrs	78.95±2.26	81.25±3.50	0.001**
3hrs	80.00±2.90	81.45±3.97	0.066+
4hrs	80.60±3.51	81.20±3.78	0.465
5hrs	81.15±3.00	80.65±3.61	0.502
6hrs	80.95±3.48	81.35±4.26	0.647
7hrs	81.85±2.88	81.55±4.09	0.705
8hrs	80.70±1.95	81.10±3.33	0.514
12hrs	80.80±3.03	81.15±3.81	0.651
24hrs	81.50±3.35	81.90±4.55	0.656

Table 4: Comparison of post-op MAP (mm Hg) in two groups of patients studied

Post-op MAP (mm Hg)	Group BC	Group LC	P value
0min	98.67±6.08	97.43±5.58	0.346
15min	98.19±7.15	97.01±4.70	0.388
30min	97.00±4.90	96.40±5.53	0.606
45min	95.19±4.12	96.07±5.84	0.434
1hrs	93.17±3.48	95.32±4.57	0.021*
2hrs	91.61±3.61	94.87±4.26	<0.001**
3hrs	92.26±3.93	94.29±3.91	0.023*
4hrs	92.25±3.64	94.60±4.03	0.008**
5hrs	93.13±2.04	93.99±3.77	0.212
6hrs	93.77±3.78	95.40±3.85	0.059+
7hrs	95.28±3.78	95.70±3.75	0.616
8hrs	95.00±3.55	95.22±3.36	0.777
12hrs	95.69±4.32	94.85±3.88	0.367
24hrs	95.78±4.47	95.63±4.65	0.877

Table 5: Comparison of post-op SpO_2 % in two groups of patients studied

Post-op SpO2%	Group BC	Group LC	P value
0min	98.05±0.22	98.33±0.47	0.001**
15min	98.48±0.51	98.38±0.49	0.372
30min	98.60±0.50	98.55±0.50	0.656
45min	98.65±0.48	98.78±0.42	0.222
1hrs	98.28±0.45	98.43±0.50	0.164
2hrs	98.93±0.27	98.88±0.33	0.462
3hrs	98.33±0.47	98.38±0.49	0.644
4hrs	98.68±0.47	98.63±0.49	0.644
5hrs	98.65±0.48	98.50±0.51	0.179
6hrs	98.33±0.47	98.55±0.50	0.043*
7hrs	98.40±0.50	98.58±0.50	0.120
8hrs	98.33±0.47	98.25±0.44	0.465
12hrs	98.38±0.49	98.35±0.48	0.819
24hrs	98.78±0.42	98.80±0.41	0.788

Discussion

Clonidine hydrochloride, an imidazoline derivative was originally developed as a nasal decongestant and vasoconstrictor. Its hypotensive and bradycardic effects were first appreciated in 1962. It is a centrally acting adrenergic agonist that lowers blood pressure by decreasing basal sympathetic nervous system activity. It was introduced first in Europe in 1966 and subsequently in the U.S. for use as an antihypertensive agent. Clonidine hydrochloride exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2- imidazoline hydrochloride [6].

Clonidine is a centrally acting selective partial adrenergic agonist (alpha-2: alpha- 1=220:1). Alpha-2 receptors are found densely in the pontine locus coeruleus which is an important source of sympathetic nervous system innervation of the forebrain and a vital modulator of vigilance.

The sedative effects evoked by alpha-2 agonists most likely reflect inhibition of this nucleus. Clonidine also stimulates alpha-2 adrenergic inhibitory neurons in the medullary vasomotor centre. As a result, there is a decrease in the sympathetic nervous system outflow from the central nervous system (CNS) to the peripheral tissues. This causes central and peripheral attenuation of sympathetic outflow and central activation of non-adrenergic imidazoline preferring receptors. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and a decrease in systolic blood pressure, heart rate and cardiac output. The ability of clonidine to modify the potassium

channels in the CNS and thereby hyperpolarize the cell membranes may be the mechanism for profound decrease in anaesthetic requirements produced by clonidine. Neuraxial placement of clonidine inhibits spinal substance P release and nociceptive neuron firing produced by the noxious stimulation. Alpha-2 afferent terminals are situated centrally and peripherally, in the superficial laminae of the spinal cord and several brain stem nuclei. This suggests that clonidine's analgesic effects are more pronounced after neuraxial administration. Clonidine synchronously decreases the cold response threshold while slightly increasing the sweating threshold thus suggesting that it acts on the central thermoregulatory system.

Jean eledjam *et al*. [7] in 1991 carried out a study to know the effect of α-adrenergic agonists on brachial plexus block comparing. Clonidine and Epinephrine. The study included 60 patients undergoing upper limb surgeries who were randomly divided into two groups of 30 patients each. Group 1 received 40 ml of 0.25% Bupivacaine + 150µg Clonidine, and Group 2 received 40 ml 0.25% Bupivacaine + 200µg Epinephrine. Patients with history of respiratory, cardiac, hepatic, and renal failure, pregnant women, patients with contraindication to study drugs, patients with contraindication to brachial plexus block were excluded from the study. Brachial plexus block was performed with supraclavicular technique.

The criteria's which were assessed was time of onset of sensory blockade (SB), time of onset of motor blockade (MB), duration of analgesia and the quality of analgesia. Patients were also monitored for SBP, DBP, HR. The sensory block onset in group 1 was 13.0±1.4 and in group 2 was 15.3±1.2. The motor block onset in group 1 was 17.9±2.8 and in group 2 was 18.5±2.1. Thus there was no difference in onset of sensory and motor blockade between two groups. The total duration of satisfactory analgesia was longer in clonidine group than with epinephrine group (728.3±35.8 vs 994.2±34.2 min; $p< 0.001$) No difference were noted regarding HR and BP in both the groups.

The study concluded that clonidine produces a longer duration of analgesia than epinephrine when injected with bupivacaine into the brachial plexus sheath, without any major adverse effects.

Dorothee M *et al*. [8] in 1992, carried out a study to know the effect of Clonidine with Lidocaine on the C–fibres action potential. In this study, isolated rabbit vagus nerve was subjected to mixture of Clonidine and Lidocaine and also different concentration of Clonidine. The action potentials were analysed with regard to peak amplitude, time to peak from beginning of stimulation, and area under the curve. Results were presented as per cent of preceding control values for action potential amplitude and area, and as delay from control with regard to time of peak amplitude. Clonidine at 500 µM caused C-fibre inhibition as 500µM Lidocaine. However, different degrees of inhibition of conduction velocity were observed, with Lidocaine causing a more pronounced slowing of action potential peak than Clonidine. Lidocaine like other local anaesthetics inhibits action potential via binding to membrane sodium channels, leading to a reduction in inward sodium currents. Whether Clonidine acts by a similar mechanism as Lidocaine could not be addressed in this study. The physical-chemical properties of Clonidine, which has a molecular weight of 230 D and pka of 8.05, are comparable to Lidocaine, which has a molecular weight of 234 D and pka of 7.9. Thus an action of Clonidine similar to that of local anaesthetic at the sodium channel is not excluded. Clonidine cannot be expected to serve as a local anaesthetic, despite its local anaesthetic effect. Supraclinical doses of Clonidine would have to be used to obtain peripheral nerve block. However the combination of low dose of Clonidine (150µg) with local anaesthetic for peripheral nerve block in the clinical setting prolongs block duration and postoperative analgesia. This effect might be due to clonidine mediated activation of post synaptic adrenergic receptors leading to local vasoconstriction at the nerve, thus prolonging local anaesthetic action by decreasing systemic absorption of local anaesthetic. Another study by Dalle *et al*. [9] comparing vasoconstrictor effects of Clonidine and Epinephrine in peripheral nerve block, did not showed the vasoconstrictor action of Clonidine. The study concluded that low doses of Clonidine (500nM) enhances the effect of Lidocaine evoked inhibition of C–fibre action potential, where the dose of Clonidine used was approximately 1000 fold lower concentration than Lidocaine.

Dorottee gaumann *et al*. [10] in 1992, conducted a randomized double blind study in which 33 patients with ASA 1 and 2 scheduled for elective surgeries of hand or forearm were included in the study. The study was carried out to compare Epinephrine and Clonidine as an adjuvant to 1% Lignocaine for brachial plexus block. Onset and recovery of motor block were not different between the groups. Maximum pain score during postoperative period tended to be higher in patients who had received Clonidine (median 6: range 1-9) than in those treated with Epinephrine (mean 3.75: range 0-8.5). A median VAS value of 0 was observed until 180 minutes after block in patients treated with Clonidine and 210 minutes in patients treated with Epinephrine. VAS value was higher in patients treated with Clonidine. Sedation score was also higher in patients treated with clonidine. There was no difference in mean arterial pressure and heart rate between the two groups. The study concluded that analgesic effect with Clonidine was poorer compared to Epinephrine but clonidine may be a useful adjuvant in patients in whom Epinephrine is contraindicated.

Francois J singelyn *et al*. [11] in 1996, carried out a study to determine the minimum effective dose of Clonidine required to prolong the duration of anaesthesia and analgesia after axillary brachial plexus blockade and to assess the incidence and severity of side effects. The study was conducted among 80 patients with ASA I/II undergoing elective hand surgeries. Patients were divided into 8 groups of 10 in a randomized, double blind fashion. Axillary brachial plexus block was performed following Winnie's landmark using 40 ml 1% Mepivacaine with 1:200000 Epinephrine and various concentration of Clonidine. Group A received no Clonidine (control group), 0.1µg/kg of Clonidine was added to group B, 0.2µg/kg to group C, 0.3µg/kg to group D, 0.4µg/kg to group E, 0.5µg/kg to group F, 1µg/kg to group G, and 1.5µg/kg to group H. The total dose of Clonidine (mean and range) administered in each group were 7.4 µg (5.5–9.4) in group B, 12.7µg (10-15.8) in group C, 18.9µg (15-24.5) in group D, 28.2µg (21.6-31.6) in group E, 34.1µg (25.5-41.5) in group F, 63.2µg (50-97) in group G and 110.4µg (100-135) in group H. The onset time, defined as the time between injection and complete anaesthesia was not statistically significant between the groups. The mean duration of sensory anaesthesia among various groups were

227±32 in group A, 239±52 in group B, 258±57 in group C, 264±63 in group D, 265±39 in group E, 314±60 in group F, 305±67 in group G, 302±24 in group H. Although there was an increase in mean sensory duration in higher doses of Clonidine, the linear trend in duration of anaesthesia at doses of 0.5,1,1.5 µg/kg was not significant, indicating no more increase in duration of anaesthesia with increase in dose they recommended dose of 0.5µg/kg. At this dose, Clonidine may be used without important reported adverse effects.

Randomized clinical studies conducted by Chakraborty *et al*. [12] which studied efficacy of bupivacaine with clonidine in supraclavicular brachial plexus block reported a higher sedation score in clonidine group but no difference in hemodynamic parameters. Similar findings were observed by Gupta *et al*. [13] who compared the effects of clonidine as adjuvant to Levobupivacaine in supraclavicular brachial plexus block. Many studies have shown hemodynamic adverse events Culebras *et al*. [14] who studied efficacy bupivacaine with clonidine in interscalene block observed no benefit in terms of postoperative analgesia or duration of the block they also noted significant reduction in mean arterial pressure and heart rate with clonidine group. Similar findings were observed by pinto *et al*. [15] in cervical plexus block for carotid endarterectomy and with Erlacher *et al*. [16] who compared 0.75% ropivacaine in axillary perivascular block. However no such adverse hemodynamic events were observed in our study.

Conclusion

To conclude, no significant difference was found in both groups in terms of Post operative hemodynamic variables

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