Original Article

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A Study on Efficacy of Clonidine and Dexmedetomidineas Adjuvants with 0.5% Levobupivacaine in Ultrasound Guided Axillary Brachial Plexus Block for Upper Limb Orthopedic Surgeries

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Abstract

Introduction: Clonidine, the older drug is a selective α-2 adrenergic agonist with some α-1 agonist property. In clinical studies, the addition of clonidine to local anesthetic solutions has shown produce anti-nociception and enhance the effect of local anaesthetics. *Methodology:* This study was conducted on 80 patients undergoing upper limb surgeries aged between 20 to 60 years under ultrasound guided axillary brachial plexus block at Medical College Hospital. Informed written consent was taken. *Results:* Statistical analysis of sedation score by Chi-square test showed that the difference in sedation score was significant (P <0.05) at 30 and 60 min. The difference in sedation score at 15 min is not statistically significant though few subjects in both the groups were sedated (P >0.05). *Conclusion:* In conclusion, when compared to clonidine (1μg/kg), dexmedetomidine (1μg/kg) has a superior clinical profile as adjuvant to levobupivacaine (0.5%) in axillary brachial plexus block.

Keywords: Clonidine; Dexmedetomidine; Levobupivacaine.

Introduction

"For all the happiness mankind can gain is not in pleasure but in rest from pain"- John Dryden. Regional anaesthetic techniques are as successful as general anaesthesia in alleviating pain during various surgical procedures. There are many advantages of a single shot PNB (Peripheral Nerve Block) like rapid onset, predictable and dense anaesthesia, a relatively simpler technique, good muscle relaxation, adequate postoperative analgesia and sympathetic block. The sympathetic block decreases postoperative pain, vasospasm and oedema. It also means early ambulation, early oral intake, avoiding intubation and its complications with lesser systemic side effects and fewer postoperative effects.

Among the various PNB, Brachial Plexus Block (BPB) is one of the most commonly practiced blocks. The various local anaesthetics used in axillary block are quite effective but the duration of analgesia is a major limiting factor. There has always been a search for adjuvants which can be added to the local anaesthetics in peripheral nerve block to improve the duration and quality of analgesia but without producing any major adverse effects. Various studies have investigated several adjuncts, including opioid, neostigmine, hyaluronidase, dexamethasone etc [1-3].

Since their synthesis, α-2 adrenergic receptor agonists have been used intrathecally, epidurally or as part of peripheral nerve blocks either alone or in conjunction with local anaesthetics in an attempt to prolong the duration of analgesia and to improve the quality of the block.

Clonidine, the older drug is a selective α-2 adrenergic agonist with some α-1 agonist property. In clinical studies, the addition of clonidine to local anesthetic solutions has shown produce anti-nociception and enhance the effect of local anaesthetics. Clonidine produces this effect by reduction in the onset time of the block and a more efficient peripheral nerve block with longer post operative analgesia. Dexmedetomidine, the newer drug, is a potent α-2 adrenoceptor agonist, and about eight-times more selective towards the α-2 adrenoceptor than clonidine. In previous clinical studies, administration of intravenous dexmedetomidine has shown to produce significant opioid sparing effects as well as a decrease in inhalational anaesthetic requirements. In humans, it has been used in various strengths as an adjunct to local anaesthetics to prolong the duration of block and postoperative analgesia in various peripheral blocks [4].

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Very few studies have compared dexmedetomidine with clonidine with respect to duration of block and postoperative analgesia especially as an adjuvant to levobupivacaine 0.5%. Keeping their pharmacologic interactions and other beneficial properties, we planned a double blind prospective randomized clinical study at our institute with an aim to evaluate and compare the onset and duration of sensory and motor blockade, duration of analgesia and sedation score by both these drugs when used in axillary brachial plexus block as adjuvants to levobupivacaine in patients undergoing upper limb orthopedic surgeries.

The Brachial plexus blocks provide a useful alternative to general anaesthesia for upper limb surgeries. They achieve near ideal operating conditions by producing complete muscular relaxation, maintaining stable intraoperative haemodynamic condition and sympathetic block.

The application of ultrasound technique for exact localization of nerves has revolutionized the regional anaesthesia field and is becoming increasingly popular as it increases success rates, shortens block onset time and reduces the number of needle insertions and complications [5].

Levobupivacaine is a long acting local anaesthetic, S(-)– enantiomer of racemic bupivacaine. When compared with bupivocaine it produces less vasodilation, so less hypotensive episodes, less CNS toxicity, less negative inotropic effect and less prolongation of QTc interval and hence higher toxic threshold

Methodology

This study was conducted on 80 patients undergoing upper limb surgeries aged between 20 to 60 years under ultrasound guided axillary brachial plexus block at Medical College Hospital.

Informed written consent was taken. Result values were recorded using presetproforma.

Inclusion Criteria

- ASA Class I and II
- Age between 20 to 60 years
- SBP - 100-140 mm of Hg
- DBP - 60-90 mm of Hg

Exclusion Criteria

- ASA Class III and IV
- Patients with medical complications like severe anemia, severe hypovolumia, shock, septicemia
- Abnormal CT, BT or anticoagulant therapy
- Local infection at the site of proposed puncture for axillary block
- History of drug allery to local anaethetics, clonidine, or dexmedetomidine
- Patient refusal

The procedure of the technique and the development of sensory and motor block were explained to the patient to ensure good co-operation

Technique

The technique, ultrasound guided axillary brachial plexus, was conducted in the major operation theatre.

Group LC: (n=40) receive 25ml of 0.5 % of levobupivacaine +1 µg/kg of clonidine , the whole solution made 30 ml by adding sterile water for injection

Group LD: (n=40) receive 25ml of 0.5 % of levobupivacaine + 1µg/kg of dexmedetomidine, the whole solution made 30 ml by adding sterile water for injection.

Sedation score was assessed using 5 point sedation scale. The scoring was recorded as follows:

1= Awake and alert.

2= Sedated but responding to verbal stimulus.

3= Sedated, responding to mild physical stimulus

4= Sedated, responding to moderate or strong physical stimulus

5= Not arousable

Intramuscular injection of diclofenac sodium 75mg was given as rescue analgesic when patient complains of pain.

Sample size calculation was based on pilot study of 10 patients and was selected to detect a projected difference of 20% in duration of analgesia between the groups, with a type I error of 0.05 and power of 0.8.

All the collected data was entered in microsoft excel sheet. It was then transferred to SPSS (Statistical Package for Social Science) ver. 17software for statistical analysis.

• Quantitative data were analyzed by student's 't' test .

• Qualitative data were analyzed by Chi-square test.

• P value <0.05 was considered statistically significant.

Results

Eighty ASA class I and II patients of either sex, aged between 20-60 years, posted for upper limb surgeries under ultrasound guided axillary brachial plexus block were selected for the study. The study was undertaken to evaluate and compare the efficacies of dexmedetomidine with that of clonidine as adjuvants to newer local anaesthetic levobupivacaine in brachial plexus block by ultrasound guided axillary approach.

The minimum age of the patient was 20 years and maximum age was 60 years. The mean of the patients in group LC was 39.90 ±11.41 years and in group LD was 39.60 ±11.03 years. Age incidences between two groups were comparable, i.e., there is no statistically significant difference in age incidences between groups as P value is more than 0.05.

Table 1: Age distribution of study groups

Study groups	Mean ± SD (Years)	t* Value	P Value	Significance
Group LC	39.90±11.41	0.120	0.90	**NS**
Group LD	39.60±11.03			

Student's unpaired 't' test, NS – Nothing Significant

Table 2: Patient distribution based on ASA grade

Study groups	ASA Class I	ASA Class II	Total	X^2 Value	P Value	Significance
Group LC	25 (62.5 %)	15 (37.5%)	40 (100%)	0.053	0.818	NS
Group LD	24 (60%)	16 (40 %)	40 (100%)			

X^2 – Chi-square test, NS – Nothing Significant

Table 3: Time for onset of sensory block (min)

Study group	Onset time	Mean difference	t*Value	P value	Significance
Group LC	8.80 ± 1.18	0.98	3.639	P<0.001	HS
Group LD	7.90 ± 1.21				

*Student's unpaired 't' test, HS – Highly Significant

Table 4: Time for onset of motor block (min)

Study group	Onset time	Mean difference	t*Value	P value	Significance
Group LC	13.48 ± 1.64	3.25	8.32	P<0.001	HS
Group LD	10.23 ± 1.60				

*Students unpaired 't' test, HS – Highly Significant

Table 5: Duration of sensory block (min)

Study group	Duration of block (min)	Mean difference	t*value	P value	Significance
Group LC	305.60 ± 26.61	101.9	18.29	P<0.001	HS
Group LD	407.50 ± 23.07				

*Student's unpaired 't' test, HS – Highly Significant

Table 6: Duration of motor block

Study group	Duration of block (min)	Mean difference	t*value	P value	Significance
Group LC	324.80 ± 24.65	82.3	16.49	P <0.001	HS
Group LD	407.10 ± 19.68				

*Students unpaired 't'test, HS – Highly Significant

In group LC, 62.5 % of the patients and in group LC 60% of the patients were ASA class I, where as 37.5% of patients in group LC and 40% of patients in group LD were ASA class II. Distribution of subjects based on ASA class is comparable, i.e., no significant difference was observed between the groups, as the P value is more than 0.05.

The mean time for onset of sensory block in group

LC was 8.88±1.18 min and in group LD was 7.90 ± 1.21 min. The statistical analysis by student's unpaired 't' test showed that, time for onset of sensory block in group LD was significantly faster when compared to group LC (P < 0.001).

The mean time for onset of motor block in group LC was 13.48 ±1.64 min and in group LD was 10.23 ± 1.60 min. The statistical analysis by student's unpaired 't' test showed that, time for onset of motor block in group LD was significantly faster when compared to group LC (P < 0.001).

Patients of both groups were observed for 12 hours.

The mean duration of sensory block in group LC was 305.60 ± 26.61 min and in group LD was 407.50 ± 23.07 min. The statistical analysis by student's unpaired 't' test showed that, time for duration of sensory block in group LD was significantly longer when compared to group LC (P < 0.001).

The mean duration of motor block in group LC was 324.80 ± 24.65 min and in group LD was 407.10 ± 19.68 min. The statistical analysis by student's unpaired 't' test showed that, duration of motor block in group LD was significantly longer when compared to group LC (P < 0.001).

Table 7: Duration of analgesia (min)

Study group	Duration of analgesia	Mean difference	t*Value	P value	Significance
Group LC	345.92±23.77	111.58	21.16	P<0.001	HS
Group LD	457.50±23.37				

*Students unpaired 't' test, HS – Highly Significant

Table 8: Sedation score

Time of assessment	Scores*	Group LC (%)	Group LD (%)	X^2 Value, Significance
0 min	1	40(100)	40(100)	-
	2	0(0)	0	No Difference
	3	0	0	
5 min	1	40(100)	40(100)	-
	2	0	0	No Difference
	3	0	0	
15 min	1	32(80)	29(72.5)	X^2=0.62 P>0.05(P=0.4)
	2	8(20)	11(27.5)	(Non Significant)
	3	0(0)	0(0)	
30 min	1	25(62.5)	9(22.5)	X^2=16.02
	2	15(37.5)	25(62.5)	P<0.05
	3	0	6(15)	(Significant)
60 min	1	20(50)	9(22.5)	X^2=6.69
	2	17(42.5)	25(62.5)	P<0.05
	3	3(7.5)	6(15)	(Significant)
2 hrs	1	40(100)	40(100)	-
	2	0(0)	0(0)	No Difference
	3	0(0)	0(0)	
6 hrs	1	40(100)	40(100)	-
	2	0(0)	0(0)	No Difference
	3	0(0)	0(0)	
12 hrs	1	40(100)	40(100)	-
	2	0(0)	0(0)	No Difference
	3	0(0)	0(0)	

X^2- Chi-square test

The mean duration of analgesia in group LC was 345.92 ± 23.77 min and in group LD was 457.50 ± 23.37 min. The statistical analysis by student's unpaired 't' test showed that, duration of analgesia in group LD was significantly longer when compared to group LC(P < 0.001).

In both the groups patients are awake and alert and hence had sedation score 1 at 0 min, 5 min, 2hours, 6 hours and 12 hours. Whereas sedation is observed between 15 min and 60 min from the time of drug injection in both the groups.

At 15 min, in group LC, 20% of patients are sedated (with sedation score 2), where as in group LD, 27.5% of patients were sedated (with sedation score 2).

At 30 min, in group LC, 37.5% of patients were sedated (with sedation score 2), where as 85% of patients were sedated (62.5% of patients with sedation score 2 and 15% of patients with sedation score 3) in group LD.

At 60 min, in group LC, 50% of patients were sedated (42.5% of patients with sedation score 2 and 7.5% of patients with sedation score 3), and in group LD, 77.5% of patients were sedated (62.5% of patients with sedation score 2 and 15% of patients with 3).

None of the patients had sedation score 4 and above during the study period.

Statistical analysis of sedation score by Chi-square test showed that the difference in sedation score was significant ($P < 0.05$) at 30 and 60 min. The difference in sedation score at 15 min is not statistically significant though few subjects in both the groups were sedated ($P > 0.05$).

Discussion

The key to successful regional anesthesia is deposition of local anesthetic accurately around the nerve structures. Electrical stimulation or paresthesia, both are relied on surface landmarks identification. However, the limitations of landmark techniques like variations in anatomy and orientation, as well as equipment accuracy, have an effect on success rates and complications. Use of ultrasound for nerve block has overcome these limitations and also shortened the mean time taken for the procedure to administer a block.

An attempt has been made to assess and compare the efficacy of clonidine and dexmedetomidine as an adjuvant to local anaesthetic levobupivacaine in ultrasound guided axillary brachial plexus block in terms of onset time and duration of sensory and motor block, duration of analgesia and sedation. Haemodynamic variables also studied.

A total of 80 patients within the age group of 20-60 years were included in the study. They were randomly divided into two groups, 40 in each group. With levobupivacaine, group LC received clonidine, where as other group, group LD received dexmedetomidine. Both groups were comparable in terms of mean age, sex ratio and ASA class ($P > 0.05$).

Peripheral Action of Clonidine

There have been four proposed mechanisms for the action of clonidine in peripheral nerve blocks. These mechanisms are centrally mediated analgesia, $\alpha_2\beta$ adrenocept or-mediated vasoconstrictive effects, attenuation of inflammatory response and direct action on peripheral nerve. The direct action of clonidine on the nerve can be explained on the basis of a study conducted by Dalle et al. [6], They proposed that clonidine, by enhancing activity-dependent hyperpolarisation generated by the Na/K pump during repetitive stimulation, increases the threshold for initiating the action potential causing slowing or blockage of conduction.

Kosugi et al. [7], examined the effects of various adrenoceptor agonists including dexmedetomidine, tetracaine, oxymetazoline and clonidine, and also an α_2 adrenoceptor antagonist (atipamezole) on compound action potential (CAP) recorded from frog sciatic nerve, and found that CAPs were inhibited by α_2 adrenoceptor agents so that they are able to block nerve conduction.

Popping et al. [8], in their metaanalysis of randomized trials showed the beneficial effect of clonidine on the duration of analgesia with all tested local anaesthetics.

There are still various studies done with clonidine as adjuvant to local anaesthetics.

El Saied et al. [9], conducted a study in which axillary brachial plexus blockade was performed with addition of clonidine to ropivacaine. The study showed that addition resulted in prolongation of sensory and motor block and analgesia without increased incidence of side effects.

In another study Giovanni Cucchiaro et al. [10], evaluated the effects of clonidine on the duration of sensory and motor block and analgesia time in children who underwent a variety of peripheral nerve blocks including brachial plexus block and concluded that the addition of clonidine to bupivacaine and ropivacaine can extend sensory and motor blocks.

Peripheral Action of Dexmedetomidine

Dexmedetomidine and clonidine are both α_2 selective agonists. It is possible that they work in a similar manner and may indicate a class effect.

A study by Brumett *e*tal. [11], showed that dexmedetomidine enhances duration of bupivacaine anaesthesia and analgesia of sciatic nerve block in rats without any damage to the nerve. The analgesic effect of peripheral perineuraldexmedetomidine was caused by enhancement of the hyperpolarisation-activated cation current, which prevents the nerve from returning from a hyperpolarized state to resting membrane potential for subsequent firing.

Kousugi et al. [12], in their study found that high concentrations of dexmedetomidine inhibit CAPs (Compound Action Potentials) in frog sciatic nerves

without α_2 adrenoceptor activation. Their result showed that dexmedetomidine reduced the peak amplitude of CAPs reversibly and in a concentration-dependent manner.

This action was not antagonized by α_2 adrenoceptor antagonists (i.e., yohimbine and atipamezole); rather, α_2 antagonists reduced the CAP peak amplitude. Clonidine and oxymetazoline, two other α_2 agonists, also inhibit CAPs. The maximum effect of clonidine was only 20%. On the other hand, adrenaline, noradrenaline and α_1 agonist phenylephrine and beta agonist isoprenaline had no effect on CAPs.

Conclusion

From our study we conclude that, the addition of dexmedetomidine (1µg/kg) as an adjuvant to levobupivacaine(0.5%) has the following advantages over clonidine (1µg/kg)

1. Faster onset of sensory and motor block
2. Prolonged duration of sensory and motor block
3. Longer duration of post-operative analgesia
4. Comfortable sedation intraoperatively without need for airway assistance

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