A COMPARATIVE EVALUATION OF DEXMEDETOMIDINE AND CLONIDINE AS ADJUVANTS TO LEVOBUPIVACAINE IN EPIDURAL ANAESTHESIA FOR LOWER LIMB ORTHOPAEDIC SURGERIES

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HOW TO CITE THIS ARTICLE:

Karthik G. S, Sahajananda H, S. Rangalakshmi, Sudheer R. "A Comparative Evaluation of Dexmedetomidine and Clonidine as Adjuvants to Levobupivacaine in Epidural Anaesthesia for Lower Limb Orthopaedic Surgeries". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 12, February 09; Page: 1955-1969, DOI: 10.14260/jemds/2015/284

ABSTRACT: BACKGROUND: There are always efforts to find a better and safer local anaesthetic along with adjuvants in epidural anaesthesia. Bupivacaine is a long acting, effective local anaesthetic that is commonly administered in anaesthesia practice. Despite its undoubted efficacy, bupivacaine is associated with cardiotoxicity and neurotoxicity. Central nervous system (CNS) and cardiovascular adverse reactions reported after inadvertent intravascular or intravenous regional anesthesia have been linked to R (+) isomer of bupivacaine. So Levobupivacaine, the pure S (-) – enantiomer of racemic bupivacaine, was developed as an alternative to bupivacaine. Levobupivacaine is increasingly used in the clinical practice because of its safer pharmacological profile and faster protein binding rate AIM: This study was conducted to evaluate the onset and duration of analgesia, extent and duration of sensory and motor block, sedation and side effects of Dexmedetomidine and Clonidine when used as adjuvants to Levobupivacaine in epidural anaesthesia for lower limb orthopaedic surgeries. MATERIALS AND METHODS: A prospective randomized study was carried out in the department of Anaesthesia at Rajarajeswari Medical College and Hospital which included 50 adult patients between the ages of 21 and 60 years (of ASA I/II grade) who underwent lower limb orthopaedic surgeries. The patients were randomly allocated into two groups; levobupivacaine + dexmedetomidine (LD) and levobupivacaine + clonidine (LC), comprising of 25 patients each. Group LD was administered 18 ml of 0.5% epidural levobupivacaine and 1.5 μ g/kg of dexmedetomidine, while group LC received admixture of 18 ml of 0.5% levobupivacaine and 2 µg/kg of Clonidine. Onset of analgesia, sensory and motor block levels, sedation, duration of analgesia and side effects were observed. STATISTICAL ANALYSIS: The data obtained was subjected to statistical analysis using analysis of variance, student t test, chi-square test and Fisher Exact test. The Statistical Software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Sysatat 12.0 and R environment ver. 2.11.1 were also used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. The value of P < 0.05 was considered significant and P < 0.0001 as highly significant. **RESULTS:** The demographic profile, initial and post-operative block characteristics and cardio-respiratory parameters were comparable and statistically non-significant in both the groups. However, sedation scores with dexmedetomidine were better than clonidine and turned out to be statistically significant (P < 0.05). The side effect profile was also comparable with little higher incidence of nausea and dry month in both the groups which was again a non-significant entity (P >0.05). **CONCLUSION:** Dexmedetomidine is a better neuraxial adjuvant when compared to clonidine for providing early onset of sensory and motor blockade levels, adequate sedation and a prolonged post-operative analgesia with better success rate and increased patient satisfaction.

KEYWORDS: Clonidine, dexmedetomidine, epidural anaesthesia, levobupivacaine, lower limb orthopaedic surgeries.

J of Evolution of Med and Dent Sci/ eISSN- 2278-4802, pISSN- 2278-4748/ Vol. 4/ Issue 12/Feb 09, 2015 Page 1955

INTRODUCTION: It has been postulated that epidural anaesthesia reduces the perioperative surgical stress response and improves surgical outcome.

Literary evidence has established the safety of levobupivacaine over bupivacaine when used in epidural anesthesia as the incidence of various adverse outcomes is higher with the latter as compared to levobupivacaine.

As an amide local anaesthetic, the mechanism of action and pharmacodynamics of levobupivacaine are similar to those of bupivacaine. It exerts its effects through reversible blockade of neuronal sodium channels. Myelinated nerves are blocked through exposure at the nodes of Ranvier more readily than unmyelinated nerves; and small nerves are blocked more easily than large nerves. Levobupivacaine is lipid soluble and highly protein bound. The dissociation constant (PKa) of levobupivacaine is similar to that of bupivacaine & ropivacaine; but higher than that of lignocaine. Its higher lipid-solubility makes it more potent which results in a longer duration of action.⁽¹⁻³⁾

Alpha-2 adrenergic agonists have both analgesic and sedative properties when used as an adjuvant in regional anaesthesia.⁽⁴⁻¹⁰⁾ They have been reported to improve the quality of epidural anaesthesia. The anaesthetic and the analgesic requirement gets reduced to a huge extent by the use of these two adjuvants because of their analgesic properties and augmentation of local anaesthetic effects as they cause hyperpolarization of nerve tissue by altering transmembrane potential and ion conductance at locus coeruleus in the brainstem. These drugs cause minimal respiratory depression when used as adjuvants to regional anaesthesia.⁽¹¹⁻¹²⁾

Keeping their pharmacologic interactions and other beneficial properties we planned a double blind prospective randomized clinically controlled study at our institute with an aim to compare the onset of analgesia and sedative effects along with the ability to provide smooth intraoperative and post-operative analgesia by both these drugs when used epidurally as an adjuvant to levobupivacaine in patients undergoing lower limb orthopaedic surgeries.

METHODS: A prospective randomized double blind controlled study was done after taking the approval from the ethical committee of Rajarajeshwari Medical College and Hospital. 50 patients of ASA I & II physical status aged between 21-60 yrs scheduled to undergo elective lower limb orthopaedic surgeries under epidural anaesthesia were enrolled for the study and were randomly allocated into two groups based on a computer generated code.

- Group LD (n=25) = patients received 18 ml of 0.5% levobupivacaine with dexmedetomidine 1.5 μ g/kg.
- Group LC (n=25) = patients received 18 ml of 0.5% levobupivacaine with clonidine 2µg/kg.

The patients with haematological disease, ASA III or greater, bleeding or coagulation test abnormalities, severe renal or hepatic derangement, previous spine surgeries, spine abnormalities, local site infection, psychiatric diseases, diabetes, history of drug abuse and allergy to local anaesthetics of the amide type, pregnant and lactating women were excluded from the study.

Patients taking tricyclic antidepressants, any anti-psychotic drugs, opiods, anti-arrythmics, beta blockers, anticoagulants and diagnosed to have poorly controlled hypertension, hypotension, angina and cardiopulmonary disease were also not considered.

The study solutions were prepared by an anaesthesia technician not involved in the proceedings. Patients and anaesthesiologist who delivered the epidural anaesthesia were blinded by the study solutions. All patients received tablet Pantoprazole 40 mg a night before the surgery.

Pre-anaesthetic evaluation of the patients were performed a day before the surgery. A written informed valid consent was taken from all the patients. In the operation theatre, a good peripheral intravenous access was secured using 18 gauge canula. Baseline noninvasive blood pressure, pulse rate, electrocardiograph, pulse oximetry were recorded. Patients were put in sitting position and skin over the desired site were infiltrated with 2% lignocaine 2ml. Epidural spaces of L3-L4/L4-L5 interspaces were located using 18G Tuohy needle, midline approach, using loss of resistance technique and epidural catheter of 18 gauge was placed in space under aseptic precautions. After exclusion of blood in the needle with negative aspiration, 3ml of lignocaine with adrenaline 1:200000 test dose was administered to exclude intrathecal or intravascular placement of the needle Any evidence of needle or catheter entry into an epidural vein or into the CSF excluded the patient from this study. After 5 minutes of administering test dose, patients in group A received 0.5% Levobupivacaine 18 ml plus dexmedetomidine $1.5\mu g/kg$ body weight and group B received 0.5% Levobupivacaine 18ml plus clonidine $2\mu g/kg$ body weight epidurally. The surgical position was made after complete establishment of motor and sensory block.

Baseline pulse rate, respiratory rate, noninvasive blood pressure was noted. Cardiorespiratory parameters were monitored continuously and recordings were made every 5 minute until 30 min and at 10 min interval, thereafter upto 60 minute and then at 15 minute interval for the next hour and finally at 30 minute in the 3rd hour. Intraoperatively and postoperatively, incidence of bradycardia (Heart rate<50beats per minute) were treated with 0.3mg of injection atropine and hypotension (Systolic blood pressure falling more than 20% mm of Hg) were treated with injection mephenteramine 3-6 mg in bolus. Time to analgesic block at T10 dermatome i.e. time interval between the end of administration of anaesthetic and the onset of cutaneous analgesia at T10 were evaluated using midline bilateral pin prick every minute till complete loss of cutaneous sensation at T10 at which point surgery was proceeded. The bilateral pin-prick method was used to evaluate and check the sensory level. The Degree of motor block was assessed using modified Bromage scale. (0= No block, 1=Inability to raise extended leg, 2=inability to flex the knee, 3=inability to flex ankle and foot).

The following block characteristics were observed and Recorded:

- Initial period of onset of analgesia.
- The highest dermatomal level of sensory analgesia.
- The complete establishment of motor blockage.
- The time to two segment regression of analgesic level.
- Time to complete recovery.

Sedation scores were recorded just before the initiation of surgery and every 30 minutes. Level of sedation was assessed using a 5 point scale which was as follows:

- 1 = Alert and wide awake.
- 2 = Arousable to verbal commands.
- 3 = Arousable to gentle tactile stimulation.
- 4 = Arousable to vigorous shaking.
- 5 = Unarousable.

Duration of analgesia was recorded as time interval from the completion of anaesthesia to the time when the patient complained of pain. During surgical procedure adverse effects like anxiety, nausea, vomiting, dry mouth, dizziness, headache, respiratory depression, pruritis and shivering were noted. Nausea and vomiting were treated with 6 mg of intravenous ondansetron. Intravenous fluids were administered as per body weight and operative loss. All the vital and haemodynamic parameters were recorded in the recovery room also at 1, 5, 10, 20 and 30 min interval. The onset of pain was managed by top-up doses of Levobupivacaine after operation. Post operation patients were assessed at 30 min, 2 hours, 6 hours 24 hours. Intensity of post-operative pain was assessed using verbal analogue scale (0 = no pain, 10 = maximum pain). At the end of the study all data were compiled and analyzed using analysis of variance, student t test, Chi-square/Fisher Exact test. The Statistical Software namely SAS 9.2,SPSS 15.0,Stata 10.1,MedCalc 9.0.1, Sysatat 12.0 and R environment ver.2.11.1 were also used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. The value of P < 0.05 was considered significant and P < 0.0001 as highly significant.

STUDY DESIGN: A Comparative two group study.

Diamania		Gro	up LD	Group LC	
	Diagnosis	No.	%	No.	%
1.	Anterior cruciate ligament tear	2	8.0	2	8.0
2.	Avascular necrosis of right hip	1	4.0	0	0.0
3.	Avascular necrosis of left hip	0	0.0	1	4.0
4.	Compound fracture right tibia and fibula	1	4.0	0	0.0
5.	Fracture both bones left leg	1	4.0	1	4.0
6.	Fracture both bones lower limb	0	0.0	1	4.0
7.	Fracture Femur	2	8.0	5	20.0
8.	Fracture left hip	1	4.0	4	16.0
9.	Fracture Left Shaft of Femur	1	4.0	0	0.0
10.	Fracture neck of femur	9	36.0	8	32.0
11.	Left fracture femur	1	4.0	0	0.0
12.	Left hip Avascular necrosis	1	4.0	0	0.0
13.	Left Intertrochanteric fracture femur	3	12.0	1	4.0
14.	Sub trochanteric fracture right femur	1	4.0	1	4.0
15.	Supracondylar Fracture left femur	1	4.0	1	4.0
	Total	25	100.0	25	100.0
	Table 1: Diagnosis in two groups of patients studied				



Surgery Underwont		Group LD		oup LC	
Surgery Underwent	No	%	No	%	
ACL Reconstruction	2	8.0	0	0.0	
Bipolar hemi arthroplasty	3	12.0	9	36.0	
DHS	1	4.0	1	4.0	
THR	3	12.0	1	4.0	
ORIF	13	52.0	7	28.0	
PFN	3	12.0	5	20.0	
Reconstruction	0	0.0	2	8.0	
Total	25	100.0	25	100.0	
Table 2: Surgery Underwent in two groups of patients studied					

ACL- anterior cruciate ligament, DHS-dynamic hip screw, THR-total hip. Replacement, ORIF-open reduction and internal fixation, PFN-proximal femur. Nailing, LD-levobupivacaine+ dexmedetomidine, LC-levobupivacaine +clonidine.



Ago in voors	Gro	oup LD	Gro	oup LC	
Age in years	No	%	No	%	
21-30	6	24.0	2	8.0	
31-40	5	20.0	1	4.0	
41-50	6	24.0	8	32.0	
51-60	8	32.0	14	56.0	
Total	25	100.0	25	100.0	
Mean ± SD	42.48±11.59 46.88±8.8			88±8.87	
Table 3: Age distribution of patients studied					

Samples are age matched with P=0.137, LD-levobupivacaine+ dexmedetomidine, LC-levobupivacaine+ clonidine.



Woight (kg)	Gr	Group LD		oup LC	
weight (kg)	No	%	No	%	
41-50	2	8.0	2	8.0	
51-60	4	16.0	3	12.0	
61-70	14	56.0	13	52.0	
71-80	5	20.0	7	28.0	
Total	25	100.0	25	100.0	
Mean ± SD 65.40±7.54 66.80±7.77					
Table 4: Weight (kg) distribution in two groups of patients studied					

P=0.521, Not significant, LD-levobupivacaine+ dexmedetomidine, LC-levobupivacaine +clonidine.

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ASA Crado	Gro	oup LD	Gr	oup LC	
ASA GIAUE	No	%	No	%	
Grade I	17	68.0	15	60.0	
Grade II	8	32.0	10	40.0	
Total	25	100.0	25	100.0	
Table 5: ASA Grade in two groups of patients studied					

P=0.556, Not significant, LD-levobupivacaine+ dexmedetomidine, LC-levobupivacaine+ clonidine.



		Group LD		Group LC	
Total duration of surgery(min)	Gro No 1 8 11 5 25 82.5	%	No	%	
61-70	1	4.0	4	16.0	
71-80	8	32.0	9	36.0	
81-90	11	44.0	12	48.0	
91-100	5	20.0	0	0.0	
Total	25	100.0	25	100.0	
Mean ±SD	82.5	55±5.64	79.6	68±6.62	
Table 6: Total duration of surgery (min) in	n two g	groups of p	oatient	s studied	

P=0.104, Not significant, LD-levobupivacaine +dexmedetomidine, LC-levobupivacaine+ clonidine.



Graph 6

Initial Block Characteristics	Group LD	Group LC	P value	
Onset time of sensory block at T10 (in minutes)	8.14±1.17	10.35±1.22	< 0.001**	
Maximum sensory block level	T6-7	T7-8	< 0.001**	
Time to maximum sensory block level(in minutes)	12.68±1.40	17.15±1.35	< 0.001**	
Time in minutes for complete motor block	15.58±1.74	24.00±1.18	< 0.001**	
Mean Total dose of Mephenteramine requirement(mg)	14.16±4.52	12.36±3.81	0.134	
Table 7: Comparison of initial block characteristics in both the groups				

P<0.001-S, LD-levobupivacaine+ dexmedetomidine, LC-levobupivacaine+ clonidine.



Graph 10

Post-op Block Characteristics(in mins)	Group LD	Group LC	P value		
Mean time to two segmental regression	135.24±5.78	127.48±3.95	<0.001**		
Mean time to regression to Bromage 1	252.44±12.48	229.80±11.37	<0.001**		
Time to first rescue top-up	345.00±13.92	317.88±5.64	<0.001**		
Total dose of Levobupivacaine used(in mg)	72.04±9.10	100.64±8.57	<0.001**		
Table 8: Comparison of post-op block characteristics in both the groups					

LD-levobupivacaine +dexmedetomidine, LC-levobupivacaine+ clonidine.



Group LD	Group LC				
(n=25)	(n=25)				
2(8.0%)	8(32%)				
8(32.0%)	13(52%)				
9(36%)	4(16%)				
6(24.0%)	0(0%)				
0(0%)	0(0%)				
Table 9: Comparison of intra-operative sedation					
scores in patients of group LD and group LC					
	Group LD (n=25) 2(8.0%) 8(32.0%) 9(36%) 6(24.0%) 0(0%) -operative set LD and grou				

P=0.004**, significant, Fisher Exact test, LD-levobupivacaine +dexmedetomidine, LC-levobupivacaine+ clonidine.



Graph 15

Side effects	Group LD (n=25)	Group LC (n=25)	P value		
Nausea	4(16%)	3(12%)	1.000		
Vomiting	1(4%)	1(4%)	1.000		
Shivering	1(4%)	2(8%)	1.000		
Headache	1(4%)	1(4%)	1.000		
Dizziness	3(12%)	2(8%)	1.000		
Dry mouth	6(24%)	7(28%)	1.000		
Respiratory depression	0(0%)	0(0%)	-		
Table 10: Comparison of side effects					

LD-levobupivacaine +dexmedetomidine, LC-levobupivacaine+ clonidine.





RESULTS: 50 patients were enrolled for the study as mentioned and were randomly divided into two groups. The demographic profiles of patients in both the groups were comparable with regards to age and weight (Table 3, Table 4). The distribution as per the ASA status were similar in both the groups and mean duration of surgery was comparable in both the groups and statistically non-significant(P > 0.05) (Table 5).

Addition of dexmedetomidine to Levobupivacaine resulted in earlier onset (8.14 ± 1.17) of sensory analgesia at T10 when compared to addition of Clonidine (10.35± 1.22). Dexmedetomidine was superior to Clonidine in providing a higher dermatomal as well as achieving maximum sensory anaesthetic level in a shorter period (12.68±1.40) as compared to Clonidine (17.15±1.35). Modified Bromage scale 3 was achieved earlier (15.58±1.74) in patients who received Dexmedetomidine as adjuvant (Table 7). Mean sedation scores were significantly higher in LD Group when compared to LC Group (P < 0.05) (Table 9). Also Dexmedetomidine provided a smooth and prolonged post-operative analgesia as compared to Clonidine. This was supported by the evidence regarding prolonged time to two segmental dermatomal regression (135.24± 5.78) (P < 0.001) as well as return of motor power to

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Bromage 1(252.44 \pm 12.48) (P <0.001)(Table 8).The LD group patients required less dose of Levobupivacaine (72.04 \pm 9.10) (P< 0.001) for post-operative analgesia during the next 24 hours.

As a result addition of dexmedetomidine to levobupivacaine in this study provided superior block characteristics along with smooth and prolonged post-operative analgesia as compared to clonidine. (Table 7)

When comparing the side effects, nothing much were noted in both the groups.

Nausea, vomiting, headache, shivering and dizziness were comparable in both the groups, thus statistically not significant (P > 0.05).we did not observe respiratory depression among patients in any of the groups (Table 10).

DISCUSSION: The use of neuraxial opioids is associated with quite a few side effects, so various options including α -2 agonists are being extensively evaluated as an alternative with emphasis on opioid-related side effects such as respiratory depression, nausea, urinary retention and pruritis. The pharmacologic properties of α -2 agonists have been extensively studied and have been employed clinically to achieve the desired effects in regional anaesthesia. Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis. Clonidine has been used successfully over the last decade for the above purpose and the introduction of dexmedetomidine has further widened the scope of α -2 agonists in epidural anaesthesia. The faster onset of action of local anaesthetics, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia into the post-operative period, dose-sparing action of local anaesthetics and stable cardiovascular parameters makes these agents a very effective adjuvant in regional anaesthesia.⁽¹³⁻¹⁸⁾

The present study was carried out to compare the clinical profile of two alpha 2 agonists dexmedetomidine and clonidine in terms of analgesic efficacy, peri-operative and post-operative, block characteristics as well as sedation effects. The demographic profile of our patients was comparable with respect to mean age, body weight, ASA grade and duration of surgery. The results in this study has shown that the addition of either 1.5 μ g/kg dexmedetomidine or 2 μ g/kg clonidine as adjuvant to epidural levobupivacaine not only prolongs the duration of analgesia but also provides a good sedation level during the surgical procedure. Dexmedetomidine is superior to clonidine as it enables an earlier onset and establishment of sensory and motor block. Further, addition of these two adjuvants promotes faster onset compared to established time of onset of sensory analgesia with levobupivacaine alone.

The results of our study clearly indicate the effectiveness of epidural dexmedetomidine as it produced profound sedation in patients of LD group when compared to patients of LC group. Overall, the sedation scores were highly significant statistically with administration of dexmedetomidine (P=0.004).

The LD group showed visible superiority over LC group in various post-operative block characteristics like the weaning of sensory and motor block, prolonged post-operative analgesia and a lesser amount of total levobupivacaine used post-operatively. The cardio-respiratory parameters remained stable throughout the study period which proves the established effects of α -2 agonists in providing a haemodynamically stable intra-operative and post-operative period. Although a slight decrease in heart rate and mean arterial pressure was observed in both the groups, it never fell down to more than 15% of the baseline values.

The side effect profile of both these drugs was quite favourable as none of the patient in either group had profound deep sedation or respiratory depression which correlates very well with other studies. Although we observed a little higher incidence of dry mouth and nausea in both the groups, it was only mildly discomforting to the patients and was mainly observed in the post-operative period and non-significant on statistical comparison.

Manal M Kamal and colleagues.⁽¹⁹⁾ found in their study that epidural dexmedetomidine is a better adjuvant than morphine when used epidurally to levobupivacaine in major abdominal surgery. Bajwa and his team.⁽²⁰⁾ found that dexmedetomidine was a better adjuvant than clonidine in epidural anaesthesia for vaginal hysterectomies.

Kumkum gupta and colleagues.⁽²¹⁾ also found that levobupivacaine with dexmedetomidine showed an earlier onset of sensory and motor blockade as compared to fentanyl during epidural anaesthesia.

Our study also emphasized that dexmedetomidine added to epidural levobupivacaine showed an earlier onset of sensory and motor blockade as compared to clonidine during epidural anaesthesia for lower limb orthopaedic surgeries.

CONCLUSION: We conclude that dexmedetomidine is a better adjuvant than clonidine in epidural anaesthesia as far as patient comfort, stable cardio-respiratory parameters, intra-operative and post-operative analgesia is concerned. Overall the experience with dexmedetomidine was quite satisfactory as compared to clonidine because of its superior sedative and anxiolytic properties during the surgical procedure under epidural anaesthesia.

Thus Dexmedetomidine added to levobupivacaine for epidural anaesthesia shortens the onset time and prolongs the duration of block as well as the duration of post-operative analgesia.

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> Date of Submission: 21/01/2015. Date of Peer Review: 22/01/2015. Date of Acceptance: 30/01/2015. Date of Publishing: 07/02/2015.