IOSR Journal Of Pharmacy *www.iosrphr.org*
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 6, Issue 4 (April 2016), PP. 13-19

"Comparative clinical study between Ropivacaine and Ropivacaine with Dexmedetomidine in Epidural Anesthesia for Abdominal Hysterectomy"

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Abstract: Background: Many techniques and drug have been tried from time to time to calm the patients and eliminate the anxiety component during regional anesthesia. Ropivacaine is a good agent for use in epidural anesthesia but having side effects like neurotoxicity and cardiac toxicity. **Aims:** This present study is designed to evaluate effects of epidural ropivacaine 0.75% and ropivacaine 0.75% with dexmedetomidine on the patients undergoing elective abdominal hysterectomy. **Settings and Design:** Randomized, prospective and comparative study **Methods and Material :** In this study, patients were randomly allocated into two groups of 30 each. Group I(R) received epidural Ropivacaine 0.75 % (17 ml) (127.5 mg) and Group II(RD) received epidural Ropivacaine 0.75 % (17 ml) (127.5 mg) with dexmedetomidine 1.5 ug/kg. Sensory, motor and hemodynamic profile between two groups was compared. **Statistical Analysis:** Mean and standard deviation was calculated. Test of analysis between 2 groups was done by't' test and chi square test then P value was calculated. **Results and Conclusion:** No significant difference was found between the groups in sensory and motor profile.($P<0.05$). Hemodynamic stability was found better with dexmedetomidine. Rescue analgesic requirement was reduced in dexmedetomidine group.

I. INTRODUCTION

Pain is a complex multidimensional human perception. The history of intrathecal and epidural anesthesia is in parallel with the development of general anesthesia. Surgical methods and the anesthetic technique have evolved and improved drastically over last two decades. Many techniques and drug have been tried from time to time to calm the patients and eliminate the anxiety component during regional anesthesia.

Ropivacaine is a first single long enantiomer- specific compound, and long acting amide local anesthetic, which has a reduced risk of cardiotoxicity, neurotoxicity and rapid recovery of motor function. Post operative pain relief is an important issue with ropivacaine; it has been used with many adjuvant for lower abdominal surgeries which has other side effects. So, our concern is of using a drug as an adjuvant with ropivacaine which provides better intra-operative hemodynamic condition as well as prolonged post operative analgesia with minimal side effects. New amide ropivacaine has minimal Cardio Vascular System and Central Nervous System toxicity as well as a lesser property of motor block during post operative epidural analgesia. Dexmedetomidine is highly selective α_2 adrenergic agonists and have both analgesic and sedative properties when used as an adjuvant in regional anesthesia. The anesthetic and the analgesic requirement get reduced to a huge extent by the use of this adjuvant because of their analgesic properties and augmentation of local anesthetic effects as they cause hyperpolarization of nerve tissue by altering transmembrane potential and ion conductance at locus coeruleus in the brain stem. It acts on both pre and post synaptic sympathetic nerve terminal and central nervous system thereby decreasing the sympathetic outflow and norepinephrine release, causing sedative, antianxiety, analgesic, sympatholytic and hemodynamic effect. [3] Dexmedetomidine does cause a manageable hypotension and bradycardia but the striking feature of this drug is the lack of opioid related side effects like respiratory depression, pruritis, nausea and vomiting. Dexmedetomidine is a new generation highly selective α_2 adrenoreceptor agonist which is dose-dependent, reduces BP, heart rate and has a sedative effect.

Keeping their pharmacologic interactions and other properties we planned a double blind prospective randomized clinically controlled study at our institute with an aim to compare the effect of epidural ropivacaine with ropivacaine combined with dexmedetomidine on the time of onset, level of sensory and motor blockade,

intensity of motor block, duration of analgesia, duration and level of sedation, hemodynamic parameter and complications in patient undergoing abdominal hysterectomy.

II. AIMS AND OBJECTIVES

This present study is designed to evaluate effects of epidural ropivacaine 0.75% and ropivacaine 0.75% with dexmedetomidine on the patients abdominal hysterectomy.
Following are the aims and objectives of my present study:-
1: Onset of sensory and motor blockade
2: Level of sensory and motor blockade
3: Intensity of motor blockade (Bromage scale)
4: Duration of analgesia (VAS score) and Rescue analgesia
5: Duration of sedation (Ramsay sedation scale)
6: Hemodynamic parameters
7: Complications
The period of observation (study time) was 24 hours including post operative period.

MATERIAL AND METHODS

This prospective, randomized comparative study was started after approval from ethical committee, on 60 ASA 1 and 2 adult female patients undergoing elective abdominal hysterectomy in Department of Anesthesiology, Dr. Ram Manohar Lohia Combined Hospital, Lucknow (U.P.) India.

INCLUSION CRITERIA

60 consecutive patients have been included with following inclusion criteria after pre anesthetic examination:
1- ASA grade 1 and 2
2- Age $\geq$ 30 yrs $\leq$ 70 yrs.
3- Female sex
4- Elective surgery
5- Weight $\geq$ 35 kg $\leq$ 70 kg.

EXCLUSION CRITERIA

Patient with following criteria have been excluded from the study.
1. Patient who are not willing to participate in the study.
2. Contraindication to epidural anesthesia like bleeding disorders, local infection.
3. Allergy to the drug under study.
4. Patients with severe psychiatric disorders as depression, dementia- on drugs which could interfere with the comprehension of the study.
5. Patient using α_2 antagonist.

III. RANDOMIZATION AND GROUP ALLOCATION

Patient were randomly allocated into two groups comprising of 30 patient in each group.
Group 1 (R) (n = 30): patients received epidural Ropivacaine 0.75 % (17 ml,) (127.5 mg)
Group 2 (RD) (n = 30): Patients received epidural Ropivacaine 0.75 % (17 ml) (127.5mg) with Dexmedetomidine (1.5µgm/ kg).

PROCEDURE

All the patients underwent a thorough pre - anesthetic checkup including relevant history and systemic examination.
On the day before surgery, vitals were examined and investigation reports were checked. All patients were thoroughly screened for previous medication, drug therapy for concomitant medical problems, any cardiovascular, respiratory, renal, neurological, endocrine or any other systemic disorders ruled out.

PRE- MEDICATIONS:-

Patient was prescribed Tab Ranitidine 150 mg - a night before and on the morning of the surgery.

ANESTHETIC TECHNIQUE

On arriving to operation theatre intravenous access was secured with 18 G IV cannula and 500 ml of ringer lactate was pre-loaded and non invasive monitoring as heart rate, ECG**,** Pulse oximetry (spo_2)**,** NIBP (non invasive blood pressure)**,** Respiratory rate were attached and were monitored continuously. Base line parameters were recorded. Blood pressure was measured at 5 minutes interval for first 30 minutes and thereafter every 30 minutes till completion of surgery.
An anesthesia registrar who was not involved in study has prepared drugs for epidural injection. Epidural block was performed with 18 gauge Tuohy needle into the L3-4 epidural space with the patient in the sitting

position under strict aseptic precaution and a test dose of 3ml of 2% lignocaine hydrochloride solution containing adrenaline 1:200000 was injected. The response to test dose has been observed for 4-6 minutes. Study drug (depending upon the group allocated) has been administered into epidural space. Postoperatively rescue analgesia was given on pain on VAS scale more than 6. Bradycardia was defined as HR less than 40 p/min, treated with injection atropine 0.6 mg intravenously and hypotension Systolic BP less than 90 mm of Hg, treated with injection mephentermine 6 mg.

IV. MEASUREMENT

An independent observer who was not aware of group allocation recorded all the observation. The bilateral pinprick method was used to evaluate and check the time of onset and the upper level of sensory block (pinprick test: defined as loss of sharp sensation by using pinprick, bilaterally at midclavicular line). While modified Bromage scale was used to measure the intensity of the motor blockade effect at 5, 10 , 15 , and 30 minute intervals after the epidural administration of drugs and till motor block was completely recovered. Ramsay score[5] was used to measure the sedation level during and in postoperative period. Postoperative pain was measured on visual analogue scale (VAS) (0-10).

Modified Bromage score as used by Breen et al.

Score	**Criteria**
1	Complete block (unable to move feet or knees)
2	Almost complete block (able to move feet only)
3	Partial block (just able to move knees)
4	Detectable weakness of hip flexion while supine (full flexion of knees)
5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

V. STATISTICAL ANALYSIS

Demographic data were analyzed with student 't' test for continuous variables and chi square test for categorical variables. Sensory and motor block analyzed by Mann Whitney test. The time of rescue analgesics and incidences of side effects were analyzed with Fisher's exact test. SPSS 14.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. $P<0.05$ was considered as significant.

VI. OBSERVATIONS AND RESULTS

No significant statistical difference was found among the study groups in respect of age, sex, weight, duration of surgery, ASA Grade and baseline laboratory investigations like pulse rate, mean arterial pressure and respiratory rate as shown in table 1.

All the patients belonging to group R required rescue analgesia within 24 hours of surgery however, only 50% (15/15) of the patients of group RD required rescue analgesia ($p<0.05$). The median time (interquartile range) of rescue requirement (VAS>4) in group R was 4(0.25) however, it was 7.0 (0) in group RD ($p<0.05$)

Overall respiratory score in this study population was median (interquartile range) was 14(2). Respiratory rate before surgery and 5 minutes of epidural were equal in both the groups. However, 10 minutes of epidural till the end of the surgery (4 H), respiratory rate in group R was higher than group RD. Patients of group RD have respiratory rate near to baseline till the end of the surgery (4H)

Table 1: Demographic data

	Group R (n=30)	Group RD (n= 30)	"p" Value
Age (in years) Mean ±SD	41±7.47	43±8.08	0.96
Weight(in kg) Mean ±SD	50.13 ± 3.59	52.3 ±4.64	0.14
Duration of surgery (min) Mean ±SD	53.03 ±12.82	53.3 ± 10.25	0.32
A S A Grade (1/2) Number (%)	28 (93.3%)/ 2 (6.66%)	25 (83.3%)/ 5 (16.6%)	0.23

Data are Mean±SD. No significant difference P > 0.05 SD=Standard Deviation

Table 2- Comparison of Heart Rate and Mean Arterial pressure between two Groups

	Heart Rate (Beats/min)			Mean Arterial Pressure(MAP) (mmHg)		
	Group R (Mean±SD)	Group RD (Mean ±SD)	"p" Value	Group R (Mean ±SD)	Group RD (Mean ±SD)	"p" Value
Baseline	80.6±9.7	76.2±9.3	0.08	93.5± 8.3	93.3±6.9	.915
5 Minutes	78.1 ±11.6	68.8 ±6.9	0.00	91.5±7.1	99.1±6.5	.000
10 Minutes	79.7±11.8	74.1±6.1	0.03	89.0±6.1	92.2±5.7	.043
15 Minutes	76.4 ±10.3	73.5±6.9	0.20	85.7±5.8	88.4±4.5	.046
30 Minutes	75.3±11.9	75.5±8.7	0.96	82.5± 7.8	84.8± 3.9	.143
1 Hour	79.3±11.9	76.0±9.0	0.23	81.9±6.2	82.7± 7.1	.652
2 Hour	80.2±7.3	80.0±5.3	0.72	86.4± 3.5	91.4±4.5	.000
4 Hour	77.9±7.0	75.3±6.5	0.14	91.2±5.6	90.7±4.8	.745

Data are Mean±SD. SD=Standard Deviation

TABLE 3: Onset and highest level of sensory block

	Group R (n=30)			Group RD (n= 30)		
Level / Time	T6	T8	T10	T6	T8	T10
5 min	1	3	2		1	5
8 min	7	7	6	11	10	3
10 min	3	-	1	-	-	-
15 min	-	-	-			
Total No of Patients	11	10	9	11	11	8
Time of onset Median (Interquartile range)	9 (1)			8 (1) P = 0.49		

Table 4: Intensity of Motor Block

Groups / Time	Group R (n=30)	Group RD (n= 30)	P value
Baseline	6.0 ± 0.0	6 ± 0.0	1.00
5 min	5.8 ± 0.4	5.7 ± 0.4	0.36
10 min	4.4 ± 0.5	4.2 ± 0.6	0.17
15 min	2.2 ± 0.4	2.2 ± 0.4	0.74
30 min	1.5 ± 0.5	1.2 ± 0.4	0.014
1 Hour	1.2 ± 0.4	1.0 ± 0.0	0.02
2 Hours	2.9 ± 0.8	2.0 ± 0.2	0.00
3 hours	5.2 ± 0.8	3.0 ± 0.4	0.00
4 Hours	5.9 ± 0.3	4.3± 0.5	0.00

Table 5: **Sedation score (Ramsay sedation score) presented as number of patients and analyzed by Mann Whitney test. * denotes P<0.05 vs. control**

Groups	Group R (n=30)					Group RD (n= 30)				
SEDATION	Ramsay Sedation Scores					Ramsay Sedation Scores				
TIME	1	2	3	4	5	1	2	3	4	5
During	30	-	-	-	-	-	15	13	2	-
End of surgery	30	-	-	-	-	-	6	8	10	6
6 Hours of surgery	-	12	16	2	-	-	9	10	11	-
12 Hours of surgery	16	14	-	-	-	5	21	4	-	-
24 Hours of surgery	29	-	1	-	-	15	14	1	-	-

Table 6: Various Side Effects; data are presented as numbers and analyzed by Fisher's exact test; * denotes P<0.05 vs. control.

Groups / Time	Group R (n=30)	Group RD (n= 30)	P value
Bradycardia	3	5	0.45
Hypotension	2	5	0.23
Nausea and vomiting	2	4	0.39
Shivering	11	1*	0.001

VII. DISCUSSION

The present randomized, controlled comparative study showed that dexmedetomidine when added with ropivacaine for epidural anesthesia have similar onset and level of sensory block however, prolonged motor blockade, better postoperative analgesia, hemodynamic more stable and better side effect profile in the form of less shivering. Use of adjuvant in epidural anesthesia has always been a fascinating area of academic interest. The pharmacologic properties of α_2-agonists have been employed clinically to achieve the desired effects in regional anesthesia alternative to opioids.[106-109] Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholytic. Clonidine has been used successfully over the last decade for the said purpose and the introduction of dexmedetomidine has further widened the scope of α_2-agonists in regional anaesthesia. In man, dexmedetomidine was first administered by epidural route in 1997,

associated with the lidocaine 1.5 % in patients undergoing hysterectomy, prolonging the duration of postoperative analgesia. We in our study the effects of dexmedetomidine when added with ropivacaine in epidural anesthesia during abdominal hysterectomy was compared.

In present study, dexmedetomidine when given with ropivacaine did not improve the either onset of sensory blockade or level of sensory block compared to Ropivacaine alone. Complete sensory block was found between dermatome T6 –T10 in patient of both groups. Most of the patient achieved complete sensory block in 8 minutes in RD group and R group though 4 patients of group R achieved block in 10 minutes. However, there was no significant difference found in median time (interquartile) between two groups. ($p>0.05$)

Adequate motor block (modified Bromage scale of 2) was achieved in most of the patients of either group in 30 minutes of the epidural injection. There was lower intensity of motor block with ropivacaine alone in comparison to ropivacaine and dexmedetomidine. Significant difference of intensity of motor block found after 1 hour between the groups. ($p<0.05$)

All the patients of group R were alert and non-sedated at all during and at the end of the surgery (Ramsay score 1). Whereas most of the patients in group RD were adequately sedated (Ramsay score 2-4). However six patient of group RD was deeply sedated (Ramsay score of 5) ($p<0.05$). The sedative effect of α_2-adrenoceptor agonists is mediated by its action in the locus ceruleus. Thus, after the epidural administration, the passage of the drug by menninges and its dispersion can be responsible for sedative effect. The variation in the respiratory rate was less in the dexmedetomidine group but the difference was not significant. ($p>0.05$) None of the patient in any group had respiratory depression (respiratory rate <8/ minute) or significantly decrease in oxygen saturation.

The addition of dexmedetomidine with the ropivacaine in the epidural space had led to better hemodynamic profile in terms of stabilized heart rate, systolic and diastolic pressure. There was fall in the heart rate in the dexmedetomidine group which can be attributed to α_2 agonistic activity of dexmedetomidine at the spinal level, when administered epidurally. Incidence of bradycardia and hypotension requiring intervention was less than 17% and similar in both the groups. There was progressive fall in MAP in both the groups but no difference was found at the end of surgery between the groups. Significant difference in heart rate and MAP was found at 5 and 10 minutes after block. ($p<0.05$)

The addition of dexmedetomidine with ropivacaine had led to decrease in the requirement of rescue analgesia by 50% during the 24 hour period. The potentiation of analgesia by dexmedetomidine was not only due to its selectivity to α_2 receptors but also due to its greater lipid solubility thus resulting in better penetration into menninges. The antinociceptive effect of dexmedetomidine occurs in the dose-dependent manner and has a direct relationship with its affinity to α_{2-} receptor located in the spinal cord. This synergistic activity of dexmedetomidine with ropivacaine in the prolongation of analgesia has decreased the opioid requirement as well as the incidence of unwanted side effect of respiratory depression which was never a problem with the dexmedetomidine. This finding has led to the better acceptance of epidural anesthesia as a primary anesthetic technique.

In both the groups the incidence of various side effects was not significant and did not result in the unexpected outcome. The incidence of nausea and vomiting was comparable in both the groups but the shivering was significantly lower in the dexmedetomidine group.

VIII. CONCLUSION

Dexmedetomidine has increased the duration and characteristic of sensory and motor blockade as evident by the study findings. Although, it does not have any effect on the onset of sensory blockade but has enhanced the quality of blockade, postoperative analgesia and hemodynamic stability during the perioperative period. Thus dexmedetomidine is a useful adjuvant in epidural anesthesia with ropivacaine.

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