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A Comparative Evaluation of Intrathecal Levobupivacaine with Dexmedetomidine versus Levobupivacaine in Gynecological Surgeries.

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Abstract*: Pain is the most distressing aspect of any type of surgery. Analgesic multimodalities have been used but are fragile with side effects that limit their usefulness. In this prospective randomized double blind study we have evaluated the anesthetic efficacy and safety of addition of 5 µgm dexmedetomidine to 15mg isobaric levobupivacaine in patients undergoing elective gynecological surgeries regarding time of onset, level of sensory block, intensity of motor block, duration of analgesia, haemodynamic stability and any complications. Eighty ASA I & II female patients, 30-60 yrs age scheduled for elective gynecological surgery under spinal anesthesia were divided into two groups. Patients were randomly allocated to receive either 3 ml isobaric levobupivacaine 5 mg/ml(15mg) with 5 µgm dexmedetomidine (group D, n=40) , or 3ml isobaric levobupivacaine 5mg/ml(15mg) with 0.5 ml normal saline(group S, n=40) .Time of onset &maximum upper level of sensory block was assessed by Pin prick test, Intensity of motor block by modified Bromage scale and duration of analgesia by VAS (visual analogue scale) were recorded as were any side effects such as sedation, bradycardia, hypotention, hypoxia, nausea, vomiting, shivering and respiratory depression. In group D there was faster onset of sensory block with more intensified motor block but haemodynamicaly less stable compared to group S. Levobupivacaine-dexmedetomidine combination required less top up analgesics postoperatively with minimal side effects compared to levobupivacaine-normal saline combination. Thus overall combined effect of intrathecal levobupivacaine and dexmedetomidine is superior over levobupivacaine alone.*

Keywords; *Levobupivacaine,Dexmedetomidinel,Regional anesthesia,Anesthetics techniques.*

I. Introduction

Pain is the most distressing aspect of any type of surgery. Analgesic multimodalities have been used but are fragile with side effects that limit their usefulness .Spinal anesthesia is preferred method for lower abdominal and lower limb surgery being simple to perform ,economical providing a fast onset and effective sensory and motor blockade However local anesthetics when used alone is associated with relatively short duration of action ,thus early analgesic intervention is needed in the postoperative period . Bupivacaine is available as a racemic mixture of its enantiomers, dextrobupivacaine, and levobupivacaine. In the past few years, its pure S-enantiomers ropivacaine and levobupivacaine have been introduced into clinical practice [1-4.] because of their lower toxic effects for cardiovascular and central nervous system. The clinical profile of spinal bupivacaine and levobupivacaine has been evaluated in volunteers and found to be effective in patients undergoing lower abdomen surgery,
day care gynecology procedures, inguinal hernia repair, and
lower limb procedures [5–16.]

In the current study the aim is to evaluate the role of dexmedetomidine when added to isobaric levobupivacaine 0.5% intrathecally among patients subjected to gynecological surgeries.

Although there are studies in the literature regarding lower abdominal surgeries under spinal anesthesia comparing local anesthetics and various adjuvants like opioids , clonidine & dexmedetomedine. Most of the clinical studies about the intrathecal α_2 adrenergic agonist are related to clonidine[31]. Highly selective α_2 adrenergic agonist dexmedetomidine is emerging as new adjunct to regional anesthesia ,analgesia and critical care setting[32]. Gradually evolving studies can build the evidence for its safe use in central neuraxial block[33]. On the basis of previous studies it is hypothesized that intrathecal 5µgm dexmedetomidine would produce more post operative analgesic effect with hyperbaric bupivacaine in spinal anesthesia with minimal side effects[27-30]. In this prospective randomized double blind controlled study our aim was to compare the effect of addition of dexmedetomidine to levobupivacaine on anesthesia quality, time of

onset of sensory and motor block, intensity of motor block ,duration of analgesia ,haemodynamic stability and any side effects.

II. Material & Methods

After approval of ethics committee a written informed consent was taken. This prospective double blind, randomized study was conducted at Ram Manohar Lohia Combined Hospital, Lucknow . Eighty patients of ASA I & II, 20 to 60 yrs of age, female patients undergoing elective Gynecological surgeries under spinal anasthesia were included in the study. The patients were randomly allocated into 2 groups ; Group D (n=40) received intrathecal isobaric Levobupivacaine 3ml, 0.5% (5 mg/ml) with 5µg Dexmedetomidine (0.5ml) (total 3.5 ml) and group S (n=40) received intrathecal isobaric Levobupivacaine 3ml, 0.5% (5 mg/ml) with normal saline 0.5m (Total 3.5 ml).

Exclusion criteria : Patients with known history of allergy to drug, any contraindication to spinal anesthesia, emergency surgery, patients not willing to participate in the study, hepatic and renal insufficiency.

Study Procedure: After the standard monitors were placed, intravenous access was established & patients were preloaded with 10ml/kg Lactated Ringers solution over 20 minute prior to surgery . Spinal anesthesia was performed with 25G Quincke spinal needle at L_{3-4} intervertebral space with patient in the sitting position using midline approach after confirming free flow of clear cerebrospinal fluid. Depending on the study group the injection of anesthetic solution (total 3.5ml) with cephalic orientation of spinal needle aperture was administered over 10-15 seconds The spinal needle was removed & the patient was placed in supine position .The end of injection was defined as time zero.

Noninvasive monitoring of vitals (ECG, Pulse Oximetry, heart rate, blood pressure, respiratory rate) were performed in operation theatre. Time of onset and highest level of sensory block was evaluated by pinprick method using 22G hypodermic needle. The highest level of sensory block was evaluated by pinprick at midclavicular line . Modified Bromage Scale was used to evaluate motor block. Vitals were recorded at preoperatively & then at 5 min, 15 min, 30 min, 60 min, 120min interval and then every half an hour till complete recovery . Duration of analgesia was assessed by time of administration of first injection of analgesic in the postoperative period. Need for analgesic injection was assessed by VAS. Patients satisfaction was assessed by interviewing them postoperatively wether they would like to have similar anesthesia in future if required. Incidence of hypotention ,bradycardia, respiratory depresion, nausea, vomiting, shivering,, backache, headache and urinary retention were also recorded .

Hypotension (fall ≥ 20% of baseline MAP) was treated with 5 mg increments of injection ephedrine i.v. and intravenous fluids. Criteria fof resp piratory depression was respiratory rate ≤8 bpm and oxygen saturation <92% on room air. Intra and postoperative pain was assessed on visual analogue scale (VAS: a horizontal 0 to 10 c.m. straight line with left of the line expressing no pain and the right end of line the worst pain). Duration of analgesia was scored when first rescue analgesic was required postoperatively. De Kock sedation scale was used:1=patient somnolent but responding to verbal commands;2=patient somnolent , not responding to verbal command; 3=patient somnolent; not responding to verbal command or manual stimulation.

III. Results

Results were expressed by standard methods as mean ± standard deviation. Chi-square test was applied for demographic data and haemodynamic parameters. Data obtained were tabulated and analyzed using Statistical Package for Social Science (SPSS 20.0 evaluation version). P-value was considered significant if <0.05 and highly significant if <0.001.All patients (n=80) completed the study; there was no statistical difference in patients demographics or duration of surgery as shown in(Table 1) shows the number of patients in each group undergoing different type of gynecological surgeries.

There was no significant difference between the study groups regarding mean age, weight, height, sex ratio and duration of surgery .

Table 1: Comparison of Demographic Data in Two Groups

	Group D (n=40)		Group S (n=40)		"t"	"p"
	Mean	SD	Mean	SD		
Age(in years)	49.13	7.208	49.00	10.033	0.064	0.949
Weight (in kg)	59.38	6.724	58.48	5.344	0.663	0.509
Height(in cm)	158.80	6.001	159.03	5.166	-0.180	0.858
Haemoglobin (gm/dl)	11.30	0.758	11.30	0.853	0.000	1.000
ASA Grade I II	 37(92.5%) 3(7.5%)		 33(82.5%) 7(17.5%)		0.000	1.000

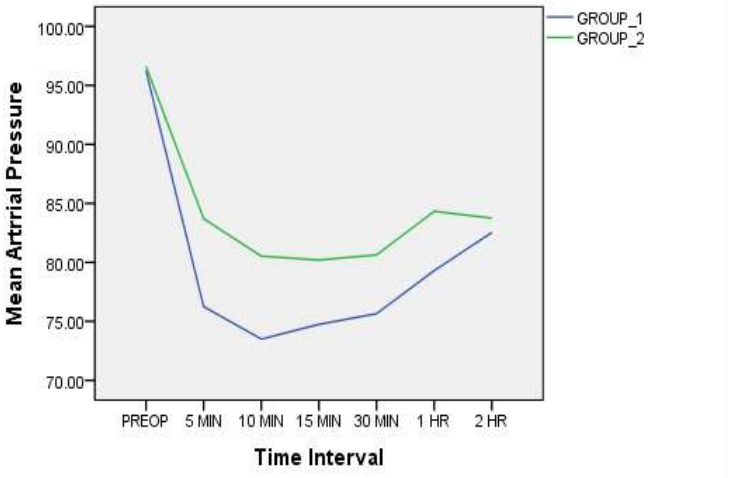
Group D showed better heart rate control throughout surgery compared to Group S. There was gradual fall in mean heart rate in group D at 10 min after subarachnoid block which came to baseline in 60 min which was not statistically significant ($p<0.05$) but in group S there remained a significant difference in intraoperative mean heart rate compared to baseline mean heart rate.

Table 2: Comparison of Heart Rate (bmp) in two groups at different time intervals

Time	Group D (n=40)		Group S (n=40)		"t"	"p"
	Mean	SD	Mean	SD		
Pre OP	87.68	6.451	83.73	7.633	2.500	0.015
5 min	85.10	6.916	83.25	7.292	1.164	0.248
10 min	81.50	7.345	82.90	5.956	-0.936	0.352
15 min	76.43	6.555	83.28	4.723	-5.362	0.000
30 min	74.80	4.842	82.73	4.466	-7.609	0.000
60 min	70.38	5.687	81.33	3.619	-10.274	0.000
120 min	66.25	4.866	80.15	3.527	-14.628	0.000

Hypotention was observe in 7 (17.5%) patients in group D while it was seen in only 3 (7.5%) patients in group S .As compared to preoperative value there was fall in MAP in both the groups but there was less fall in MAP in group S compared to D thus patients receiving intrathecal dexmedetomidin were hemodynamically less stable.

Comparison of MAP (mmHg) in two groups at different time intervals



Mean time of onset of sensory block was faster in group D (4.65± 0.976 min) than group S (6.475± 1.396 min). The maximum upper level of sensory block attained was T_6 in both the groups . Thus the mean value of upper level of sensory was comparable in both the groups.

Time of Onset and Highest level of Sensory Block

Upper Level of Sensory Block		Time of onset sensory block						
		4 min	6min	8 min	10 min	Total	t value	p value
T_6	Group D	9	8	0	0	17	-6.77625	P<0.001
	Group S	0	6	8	1	15		
T_8	Group D	8	11	1	0	20		
	Group S	2	11	7	2	22		
T_{10}	Group D	0	3	0	0	3		
	Group S	1	2	0	0	3		
Mean onset time	Group D	4.65±0.976				80		
	Group S	6.475±1.396						

In group D Grade 3 motor blockede (Modified Bromage Scale) was seen in 37 patients (n=37/40) (92.5%) and grade 2 in 3 patients (n=3/40) (7.5%). In group S 32 patients showed grade 3 motor blockade (80%), 6 patients (15%) grade 2 and 2 patients (5%) grade 1 motor blockade thus it was found that group D had more intensified motor block compared to group S (p=0.64432).

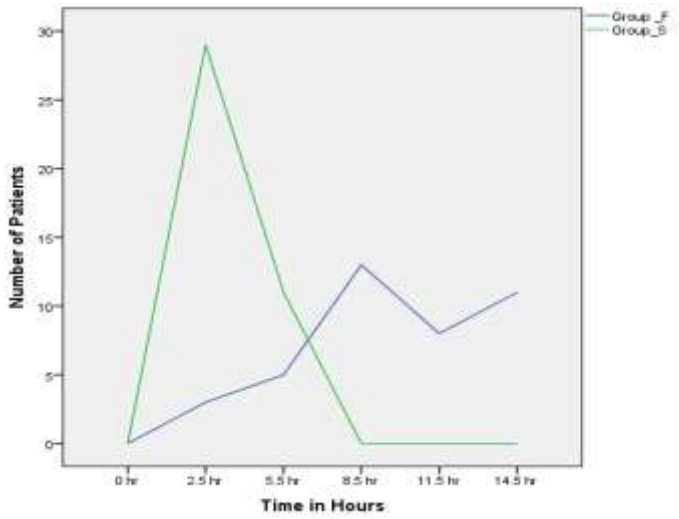
Intensity of Motor Blockade

Motor Blockade	Group D(n=40)	Group S(n=40)	Chi Square	p value
I	0	2	3.36232	0.64432
II	3	6		
III	37	32		
IV	0	0		
	0	0		
VI	0	0		

Mean duration of analgesia in group D was 9.35 (9.35+3.635) hrs while in group S it was 3.634+1.347) hrs. min. Duration of analgesia was significantly prolonged in group D than group S and also less top up analgesics were required in postoperative period in group D thus making it cost effective.

	Group D (n=40)		Group S (n=40)		"t"	"p"
	Mean	SD	Mean	SD		
Duration of Analgesia (in hour)	9.35+3.635	3.634	2.93+1.347	1.347	10.484	0.000

Duration of analgesia(in Hours)



Hypotention was the most common complication in group D observed in 7 patients (n=7/40)(17.5%) (p=). Five patients in group D (12.5%) had brdycardia while only one patient in group S had bradycardia. Two patients in group S had urinary retention and were catheterized. There was no complaint of headache , nausea, vomiting ,shivering or respiratory depression in any of the study groups.

IV. Discussion

Recent trends for gynecological surgeries show increased accptence of regional anesthesia. The mechanism by which intrathecal α_2 adrenoceptor agonist prolong the onset and sensory block of local anesthetics is speculative. It may be an additive or synergistic effect secondary to the different mechanisms of action the local anesthetics and intrathecal α_2 adrenoceptor agonist. Local anesthetics act by blocking sodium channels, α_2 adrenoceptor agonist act by binding to the presynaptic C-fibres and postsynaptic dorsal horn neurons. They produce analgesia by depressing release of C-fibre transmitters and by hyperpolarization of postsynaptic dorsal horn neurons. The complementary action of local anesthetics and α_2 adrenoceptor agonist accounts for their profound analgesic properties. The prolongation of the motor block of spinal anesthetics may be the result of binding of to the motor neurons in the dorsal horn.

Dexmedetomidine is eight times more specific and highly selective α_2 adrenoceptor agonist compared to clonidine ,thereby making it a safe adjunct in different clinical applications. Various authors has evaluated Dexmedetomidine as an epidural adjunct and found that it prolong the sensory and motor block duration time and postoperative analgesia without any additional morbidity. Clinical studies exhibits potentiation of neuraxial local anesthetics and decrease in intraoperative anesthetic requirement with prevention of intraoperative awareness, better postoperative analgesia when epidural or caudal

dexmedetomidine was used in conjunction with general anesthesia[29-31]. In this study we have used 5µg Dexmedetomidine which is based on previous human studies wherein no neurotoxic effects have been observed[18,19,27]. Kanazi et al. foun that 3µg dexmedetomidine or 30µg clonidine added to 13 mg spinal bupivacaine produced same duration of sensory and motor block with minimal side effects in urological surgical patients.

Mean time of onset of sensory block was faster in group D (4.65± 0.976 min) compared to group S (6.475± 1.396 min) in this study similar to that of Aliye Esmaoglu,Sumeyra Turk,Adnan Bayram et al[21].(2013) , Ahmed Soby Basuni, Hoda Alsaid Ahmed Ezz et al[24].(2014) and Sherif A Abdelhamid et al[23].(2013). The maximum upper level of sensory block attained was T_6 in both the groups. Thus the mean value of upper level of sensory block was comparable in both the groups. Vania Kanvee and Gadhvi Rina et al[22]. studied comparative evaluation of dexmedetomidine and clonidine as an adjunct with intrathecal isobaric levobupivacaine in spinal anesthesia stated that there is no difference in the time of onset of sensory and motor block . Kim JE and Kim NY et al[25]. observed effect of intrathecal dexmedetomidine on low dose bupivacaine spinal anesthesia in elderly patients undergoing transurethral prostectomy found that it produced fast onset of sensory and motor block.

Duration of analgesia (the time interval from subarachnoid block to first request of analgesic in postoperative period) was significantly prolonged in group D (561.0 min) compared to group S (175.80 min). We noted significantly delayed requirement of rescue analgesic and significantly reduced 24 hr. analgesic requirement with5µgdexmedetomidine when compared to group S. Prolonged perioperative analgesia after co-administration of dexmedetomidine and levobupivacaine can be explained by the complementary action of local anesthetics and α_2 adrenoceptor agonist . Aliye Esmaoglu and Sumeyra et al.[21](2013) studied the effect of dexmedetomidine added to spinal levobupivacaine for transurethral endoscopic surgery and observed that the combined use of 3 µg dexmedetomidine and levobupivacaine in spinal anesthesia prolongs sensory and motor block duration .Vania Kanvee and Gadhvi Rina et al .[22](2015) did comparative evaluation of dexmedetomidine and clonidine as an adjunct with intrathecal levobupivacaine in spinal anesthesia found that intrathecal dexmedetomidine with isobaric levobupivacaine significantly prolongs sensory and motor block and postoperative analgesia as compared to clonidine. Kim et al.[25] also stated that dexmedetomidine 3µg when added to intrathecal bupivacaine prolonged postoperative analgesia.

Dexmedetomidine evokes a biphasic blood pressure response. A short hypertensive phase and subsequent hypotension.The two phases are considered to be mediated by two different α2-AR subtypes; the α -2B In our study 7(17.5%)patients developed hypotention in the group D versus 3(7.5%) in group S and this was managed by i/v inj.ephedrine and i.v. fluids. Thus group D patients were haemodynamically less stable compared to group S. In the study of Gupta et.al[17].(2011) hypotention was more in the dexmedetomidine group than in fentanyl group but it was not statistically significant. In agreement with our results,Kanazi et al[18].showed insignificant effect of dexmedetomidine on mean blood pressure when added to intrathecal bupivacaine. Al.Mustafa et al[19]. using 5 µg ,and 10 µg dexmedetomidine ,found a dose dependent but still insignificant decrease on the mean blood pressure when compared to bupivacaine (control)group.

Patients who received intrathecal dexmedetomidine had more prolonged and intensified motor block compared to group S . Ahmed Sobhy Basuni and Hoda Alsaid Ahmed Ezz et al[24].(2014) evaluated the effect of dexmedetomidine as supplement to low-dose levibupivacaine spinal anesthesia for knee arthroscopy found that it prolonged and intensified levobupivacaine sensory and motor block. Vania Kanvee and Gadhvi Rina et al[22].(2015) did comparative evaluation of dexmedetomidine and clonidine as an adjunct with intrathecal levobupivacaine found that dexmedetomidine with isobaric levobupivacaine significantly prolongs sensory and motor block. Vidhi Mahendru et al[20]. (2013) studied the comparative evaluation intrathecal dexmedetomidine ,clonidine, and fentanyl as adjunct to hyperbaric bupivacaine for lower limb surgeries observed that intrathecal 5 µg dexmedetomidine significantly prolonged the duration of motor block.
Ramila H Jamliya and Varun Deshmukh et al[26]. Observed the effect of adding dexmedetomidine to intathecal bupivacaine and found that 15 mg hyperbaric bupivacaine supplemented with 5 µg dexmedetomidine produces prolonged motor and sensory block.

The most significant side effect reported about the use of intrathecal α2 adrenoceptor agonist are bradycardia and hypotention. In our study these are not significant probably because we used small dose of intrathecal dexmedetomidine with high dose of local anesthetics. In group D, 7 (17.5%) patients had bradycardia which responded to inj. Atropine sulphate 0.6 mg i/v while bradycardia was observed in only one patient (2.5%) in group S. Small dose of dexmedetomidine may also be responsible for minimal or no sedation in group D. No significant difference was observed in the sedation scores with patients in both the groups having score of 1. There was no incidence of respiratory depression in patients in any of the groups. Lower VAS values (<3) were observed in both the groups during the whole duration of the surgery.

This study reveals that when 5µg dexmedetomidine was added to isobaric levobupivacaine 15 mg the combination leads to faster onset , more intense sensory and motor blockade which is haemodynamically

less stable. The duration of postoperative analgesia was significantly prolonged without any remarkable side effects.

Thus overall combined effect of intrathecal levobupivacaine and dexmedetomidine is superior over levobupivacaine alone.

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Conflicts Of Interest

The authors declare that they have no conflicts of interest with the research presented in this a**rticle.**