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A Randomized Double Blind Comparative Study of Two Different Doses of Intrathecal Dexmedetomidine 5 mcg and 10 mcg AS Adjuvant to 0.5% Levobupivacaine Heavy (12.5mg) in Spinal Anaesthesia for Infraumbilical Surgery

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Abstract: ***Introduction**: Subarachnoid block is most commonly used for infraumbilical surgeries. Various adjuvants like fentanyl, clonidine and dexmedetomidine have been used for prolongation of anaesthetic effect of intrathecal levobupivacaine heavy. Different doses of dexmedetomidine have shown varying results. **Objectives**: To compare two different doses of dexmedetomidine 5 mcg and 10 mcg as an adjuvant to intrathecal levobupivacaine heavy 12.5mg in terms of onset and duration of sensory and motor block, hemodynamic effects and adverse effects in patients undergoing infraumbilical surgeries. **Methods**: Prospective, randomized, double blind study of 120 patients divided into three equal groups (40 each) named Group L, D5 and D10, of age between 18 - 60 years with ASA grade I & II undergoing infraumbilical surgeries under spinal anaesthesia was done. Intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5ml), intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5ml) with 5mcg dexmedetomidine and intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5ml) with 10mcg dexmedetomidine was given to each patient of Group L, D5 and D10 respectively. Onset and duration of sensory and motor block was noted and hemodynamic parameters were compared between these groups. **Results**: The mean time of onset of sensory and motor block was lesser in group D10 as compared to group D5 and group L ($p<0.001$). Duration of sensory and motor block was longer in group D10 as compared to group D5 and group L ($p<0.001$). Incidence of bradycardia and hypotension was seen in group D10. **Conclusion**: In the present study it was found that addition of dexmedetomidine to intrathecal levobupivacaine heavy leads to early onset of sensory and motor block as well as prolongation of their duration in a dose dependent manner.*

Keywords: Levobupivacaine heavy; Dexmedetomidine; Intrathecal.

1. Introduction

Spinal anaesthesia was initially administered by J. Leonard Corning in New York in 1885. The first deliberate use of spinal anaesthesia for surgery on a human was carried out by August Bier on August 16, 1898, in Kiel, where he injected 3 ml of 0.5% cocaine into the intrathecal space[1]. Over a century later, spinal anaesthesia remains one of the most popular techniques for both elective and emergency surgeries, including caesarean sections, lower abdominal procedures, and orthopaedic and urological surgeries[2] regional anaesthesia offers numerous advantages over general anaesthesia by eliminating both intra - operative and postoperative pain, facilitating superior muscle relaxation, and reducing intraoperative bleeding[3].

The pursuit of identifying novel and safer anaesthetic agents constitutes a fundamental imperative within the field of anaesthesiology. Levobupivacaine, distinguished as the pure S () enantiomer of bupivacaine. Various studies have indicated that the levorotatory isomers possess a pharmacologically safer profile[4] with less cardiac and neurotoxic adverse effects[5, 6]. This decreased toxicity of levobupivacaine is attributed to its faster protein binding rate[7]. The pure S (−) enantiomers of bupivacaine, i. e., ropivacaine and levobupivacaine were thus introduced into the clinical anaesthesia practice.

In an effort to further extend the duration of intra - operative and postoperative analgesia, various adjuvants such as vasoconstrictors, alpha - 2 agonists, and opioids have been utilized[8, 9] have been used. “Dexmedetomidine is highly selective alpha - 2 adreno rceptor agonists. It potentiates local anaesthetics effects, prolongs postoperative analgesia, and has a dose dependent sedative effect without respiratory depression[9].

This study is proposed to compare two different doses of dexmedetomidine 5 mcg and 10 mcg as adjuvant to levobupivacaine heavy 12.5mg in terms of onset and duration of sensory and motor block, Hemodynamic effects and adverse effects in patients undergoing infraumbilical abdominal surgery”.

Aims and Objectives

This study aims to compare two different doses of Dexmedetomidine which when added as an adjuvant to Levobupivacaine heavy in spinal anaesthesia might prolong anaesthetic effect.

This will be achieved by following observations -

1) Onset of sensory and motor block.

2) Duration of sensory and motor block.
3) Perioperative hemodynamic changes.
4) Complications (if any).

2. Material and Methods

After obtaining approval from Institutional Ethical Committee, Total 120 patients (40 patients in each group) belonging to American Society of Anaesthesiologists (ASA) physical status I – II, age group 18 - 60 yrs of either sex posted for elective infraumbilical surgery were recruited in the study. This study was prospective, randomised, double blinded study. The study was conducted over a period of one year in the Department of Anaesthesiology attached to various Operation theatres, Moti Lal Nehru Medical College and associated hospital (Swaroop Rani Nehru Hospital), Prayagraj after written and informed consent.

Sample Size: Sample size is calculated on the basis of time to bromage scale 4 from the study by Rai *et al.*[9] post operative period using the formula:

$$\text{Sample size} = \frac{r+1}{r}\frac{SD^2(Z_\beta + Z_{\alpha/2})^2}{d^2}$$

'r': number of groups; SD: pooled SD from previous study: 0.415 ZB= 0.84, Za/2=1.96; 'd'= mean difference =0.22

Sample Size (N) = 36.26 ~37 in each group.

Adding a loss to follow - up of 5%, So the required sample size, n = 39 for each group. Rounding off to nearest multiple of 3, total 120 cases (40 cases in each group).

Randomization: done on the basis of a computer generated table of random number generated by using Microsoft Excel.

Group Allocation: Total number of 120 patients of either sex selected for the study were randomly divided into Three groups:

Group L (n = 40): Intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5ml) with 0.1ml normal saline was given. They served as control.

Group D5 (n = 40): Intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5 ml) with dexmedetomidine 5µg (0.05ml) with normal saline (0.05ml) in the same syringe was given.

Group D10 (n=40): Intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5 ml) with dexmedetomidine 10µg (0.1ml) in the same syringe was given.

The volume of the drug was kept constant (2.6ml) in all groups to avoid bias in the study.

Blinding: Double blinding was done

Selection of Patients: Inclusion Criteria:
1) Patients of either sex aged between 18 and 60 years.
2) Patients scheduled to undergo elective infraumbilical abdominal surgery.
3) Patients classified as American Society of Anaesthesiologists (ASA) physical status I or II.
4) Patients giving valid informed and written consent.

Exclusion Criteria:
1) Patient refusal.
2) Patients with contraindications to spinal anaesthesia (e. g., infection at the site of injection, coagulation disorders).
3) Patients with Spine deformity.
4) Patients with a history of allergy or hypersensitivity to dexmedetomidine or levobupivacaine heavy
5) Patients with pre - existing neurologic or psychiatric disorders.
6) Patients with severe cardiovascular, respiratory, hepatic, or renal diseases.
7) Patients with a body mass index (BMI) greater than 40 kg/m².
8) Patients belonging to American Society of Anesthesiologists (ASA) physical status III or IV.

Methodology
A detailed pre - anaesthetic check - up was carried out for each patient with detailed case history, general examination, systemic examination assessment of airway and evaluation of investigation. All patients were visited a day prior to the surgery and explained in detail for the anaesthetic procedure. All patients were kept nil per oral as per NPO guidelines prior to the day of surgery and received Tab. Ranitidine 150 mg and Tab. Alprazolam 0.5 mg both orally as pre medications on day prior to surgery. Patient were randomly allocated one of three groups.

Group L - Patients in which intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5ml) with 0.1ml normal saline. They served as control.

Group D5 - Patients in which intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5 ml) with dexmedetomidine 5µg (0.05ml) with 0.05ml normal saline in the same syringe.

Group D10 - Patients in which intrathecal 0.5% levobupivacaine heavy 12.5mg (2.5 ml) with dexmedetomidine 10µg (0.1ml) in the same syringe.

The volume of the drug was kept constant (2.6ml) in all groups to avoid bias in the study.

On arrival at the operation theatre, ASA recommended standard monitors like Pulse oximeter, non - invasive blood pressure and electrocardiograph (ECG) were attached and baseline readings were taken. Intravenous (IV) access was established using an 18-gauge cannula and 10 - 20 ml/kg of intravenous Ringer Lactate was infused over 20 to 25 min prior to subarachnoid block.

Materials Used:
1) 25G Quincke Babcock type spinal needle.
2) 5 ml Syringe.
3) 1 ml Syringe.
4) Drugs –
   a) 0.5 % Levobupivacaine Heavy.
   b) Dexmedetomidine 100mcg/ml (without preservative)

5) Sterile drapes.

Patients were placed in lateral Decubitus positions on the operation table, skin was cleaned and draped. After informing the procedure to the patient, following strict aseptic techniques infiltrating the skin over the L3 - 4 or L4 - L5 interspace with 2% Lidocaine, lumbar puncture was performed at the L3 - L4 level through a midline approach using a 25 - gauge Quincke type spinal needle. After ensuring free flow of cerebrospinal fluid, the study drug was administered in the subarachnoid space over 20–30 seconds, aspirating CSF at the beginning and end of the injection to confirm needle position. The patients were placed in the supine position later on with no tilt given to the table.

Observed parameters:

a) Heart rate, Oxygen saturation (spo2), Non- invasive blood pressure (mean arterial pressure) was measured at every 5minutes for first 15minutes and then every 15 minutes for rest of surgery. Heart rate <50 bpm was considered bradycardia and treated with incremental dose of inj. Atropine 0.4mg I/V. A decrease in mean arterial pressure> 20% of the baseline blood pressure is considered hypotension and treated with incremental doses of inj. Mephentermine 6mg I/V. Oxygen supplementation was given if oxygen saturation fall below 92%.

b) Onset of sensory block was determined by the time from administration of drug to loss of pinprick sensation till T10 level (check every 1 minute from administration of drug till 15 minute by loss of sharp sensation to atraumatic pinprick with 26 gauge blunt tip needle in midclavicular line bilateral [y).

c) Onset of motor block was determined by the time from administration of drug to motor block up to Bromage 3 (check every 1 minute from administration of spinal anaesthetic drug till 15minutes assessed by Modified Bromage Motor score).

Motor block was assessed based on a Modified Bromage scale.

Bromage 0 - No motor block.

Bromage 1 - Inability to raise extended leg, able to move knees and feet. Bromage 2 - Inability to raise extended leg and move knees, able to move feet. Bromage 3 - Complete block of motor limb.

a) Duration of sensory block was defined by the time taken by sensory block regress from maximum sensory block level upto s1 dermatome level (assessed by pin prick method every 15 min fallowing intrathecal injection)

b) Duration of motor block was defined by the time taken by motor block to recover upto Bromage score 0 (was assessed every 15 minutes fallowing intra thecal injection).

6) Complication.

3. Observation and Results

Table 1: Study population randomly divided into Groups

SN	Group	Drug	No.	%
1	Group L	Levobupivacaine Heavy 12.5 mg (2.5ml) +0.1 ml NS	40	33.3%
2	Group D5	Levobupivacaine Heavy 12.5 mg (2.5ml) +Dexmedetomidine 5mcg (0.05 ml) +0.05 ml NS	40	33.3%
3	Group D10	Levobupivacaine Heavy 12.5 mg (2.5ml) +Dexmedetomidine 10mcg (0.1 ml)	40	33.4%
	TOTAL		**120**	**100%**

As shown in table 1 Total study population was divided into three equal groups.

Table 2: Intergroup comparison of Gender

SN	Gender	Group L		Group D5		Group D10	
		No	%	No	%	No	%
1	Female	19	47.5	20	50.0	21	52.5
2	Male	21	52.5	20	50.0	19	47.5
$\chi^2 = 0.200$; p=0.905							

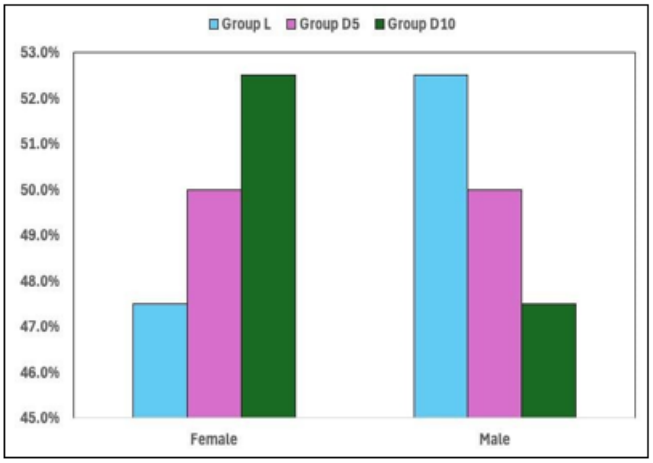

Figure 1: Bar diagram depicting intergroup comparison of Gender

As shown in table 2 and figure 2 No significant difference was found in male - female proportion among the groups (p=0.905).

Table 3: Intergroup comparison of ASA grade

SN	ASA Grade	Group L		Group D5		Group D10	
		No	%	No	%	No	%
1	I	19	47.5	21	52.5	20	50.0
2	II	21	52.5	19	47.5	20	50.0
$\chi^2 = 0.200$; p=0.905							

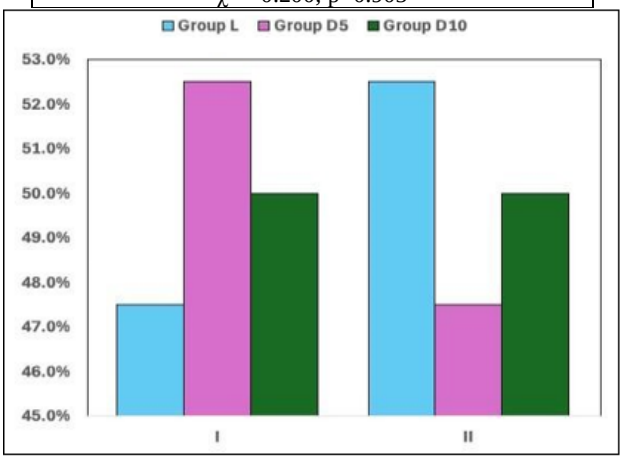

Figure 2: Bar diagram depicting intergroup comparison of ASA grade

The ASA Class I & II proportion of Group L, Group D5 and Group D10 was 47.5%: 52.5%, 52.5%: 47.5% and 50.0%: 50.0% respectively. No significant difference was found in ASA classI & class II proportion among the groups (p=0.905).

Table 4: Intergroup comparison of Heart rate at different intervals

S No.	HR	Group L		Group D5		Group D10		ANOVA	
		Mean	SD	Mean	SD	Mean	SD	F	p value
1	0 min	84.49	11.42	84.18	7.52	88.18	7.60	2.73	0.069
2	5 min	80.33	10.51	75.56	7.49	75.87	9.38	3.79	**0.025**
3	10 min	75.89	9.88	72.49	6.89	71.11	6.72	4.29	**0.016**
4	15 min	72.40	7.83	70.53	7.03	68.24	7.74	3.43	**0.035**
5	30 min	72.76	7.07	70.62	7.48	69.02	8.32	2.70	0.071
6	45 min	73.49	6.54	71.40	6.29	70.31	6.71	2.76	0.067
7	60 min	73.78	7.09	72.47	6.82	70.62	6.46	2.45	0.090
8	75 min	75.36	7.41	72.93	7.74	71.60	7.19	2.94	0.056
9	90 min	75.98	6.86	73.78	7.41	72.80	6.33	2.52	0.084
10	105 min	76.09	7.04	73.64	7.21	73.22	6.15	2.32	0.102
11	120 min	76.38	7.70	73.82	6.45	73.42	5.73	2.60	0.078

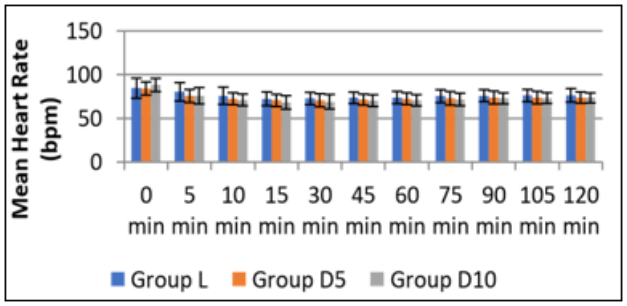

Figure 3: Bar diagram depicting intergroup comparison of Heart rate at different intervals

At baseline there was no significant difference in mean Heart rate among the three groups (p=0.069).

After that in group L, the mean Heart rate was decreased to the minimum level 72.40 ±7.83 at 15 min and then increased again and finally got the value 76.38±7.70 at 120 min.

In group D5, the mean Heart rate was decreased to the minimum level 70.53±7.03 at 15 min and then increased again and finally got the value 73.82±6.45 at 120 min

In group D10, the mean Heart rate was decreased to the minimum level 68.24±7.74 at 15 min and then increased again and finally got the value 73.42±5.73 at 120 min.

The significant difference among the groups was observed at 5 min, 10 min and 15 min.

Table 5: Intergroup comparison of Mean Arterial Pressure at different intervals

S No.	MAP	Group L		GroupD5		GroupD10		ANOVA	
		Mean	SD	Mean	SD	Mean	SD	F	p value
1	0 min	90.64	4.75	93.36	5.81	92.80	6.51	2.80	0.064
2	5 min	83.67	5.27	80.58	6.29	79.71	5.46	6.01	**0.003**
3	10 min	80.04	4.47	78.71	7.35	76.04	6.94	4.58	**0.012**
4	15 min	77.71	5.39	75.38	7.86	73.11	7.45	4.88	**0.009**
5	30 min	78.53	5.40	76.78	7.19	75.64	6.27	2.38	0.097
6	45 min	78.69	4.12	76.98	6.07	75.87	7.09	2.62	0.076
7	60 min	80.33	4.30	77.58	5.04	78.31	7.11	2.91	0.058
8	75 min	80.71	4.07	78.13	5.18	79.16	6.76	2.56	0.081
9	90 min	80.62	4.29	78.67	5.24	78.69	6.35	1.98	0.143
10	105 min	81.78	4.06	79.80	4.75	80.00	6.42	1.99	0.140
11	120 min	82.04	5.12	81.20	4.94	79.69	6.35	2.11	0.125

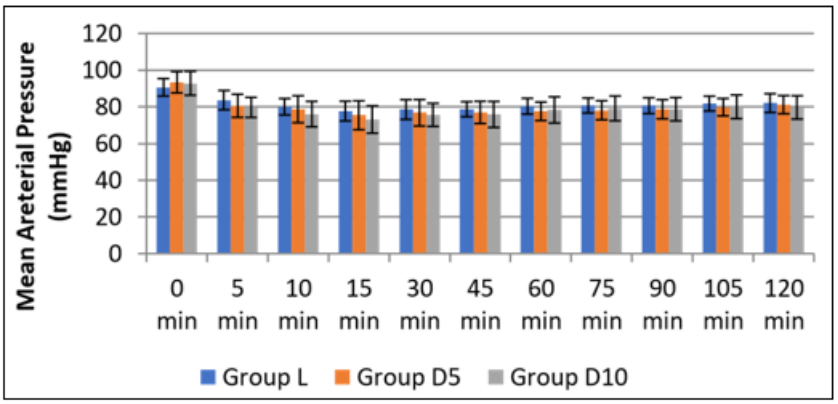

Figure 4: Bar diagram depicting intergroup comparison of Mean Arterial Pressure at different intervals

At baseline there was no significant difference in mean MAP among the three groups (p=0.064). After that in group L, the mean MAP was decreased to the minimum level 77.71±5.39 at 15 min and then increased again and finally got the value 82.04±5.12 at 120 min.

In group D5, the mean MAP was decreased to the minimum level 75.38±7.86 at 15 min and then increased again and finally got the value 81.20±4.94 at 120 min.

In group D10, the mean MAP was decreased to the minimum level 73.11±7.45 at 15 min and then increased again and finally got the value 79.69±6.35 at 120 min

The significant difference among the groups was observed at 5 min, 10 min and 15 min.

Table 6: Intergroup comparison of Onset of Sensory Block

SN	Parameter	Group L		Group D5		Group D10		ANOVA	
		Mean	SD	Mean	SD	Mean	SD	F	'p'
1	Onset of Sensory Block	4.97	0.58	3.48	0.52	2.81	0.43	187.495	<0.001

The mean onset of sensory block of group L was maximum (4.97 ± 0.58 min) and minimum in group D10 (2.81 ± 0.43min) and in group D5 (3.48 ± 0.52min). The significant difference was found in mean onset of sensory block between the groups (p<0.001).

Table 7: Intergroup comparison of Onset of Motor Block

SN	Parameter	Group L		Group D5		Group D10		ANOVA	
		Mean	SD	Mean	SD	Mean	SD	F	'p'
1	Onset of Motor Block	5.81	0.76	4.33	0.68	3.40	0.44	142.620	<0.001

The mean onset of motor block of Group L was maximum (5.81 ± 0.76 min) and minimum in group D10 (3.40 ± 0.44 min) and in group D5 (4.33 ± 0.68min). The significant difference was found in mean onset of motor block between the groups (p<0.001).

On comparing statistically, onset of Motor and Sensory block, Group D10 has significantly early onset of both motor and sensory block as compared to the other two groups.

Table 8: Intergroup comparison of Duration of Sensory Block

SN	Parameter	Group L		Group D5		Group D10		ANOVA	
		Mean	SD	Mean	SD	Mean	SD	F	'p'
1	Duration of Sensory Block (min)	169.23	9.50	235.25	7.16	276.63	9.77	1487.207	<0.001

The mean duration of sensory block of group D10 was maximum (276.63 ± 9.77 min) and in group D5 D10 (235.25 ± 7.16min) and minimum in group L (169.23 ± 9.50min) The significant difference was found in mean duration of sensory block between the groups (p<0.001).

Table 9: Intergroup comparison of Duration of Motor Block

SN	Parameter	Group L		Group D5		Group D10		ANOVA	
		Mean	SD	Mean	SD	Mean	SD	F	'p'
1	Duration of Motor Block (min)	139.5	10.49	196.25	9.66	236.25	9.39	973.276	<0.001

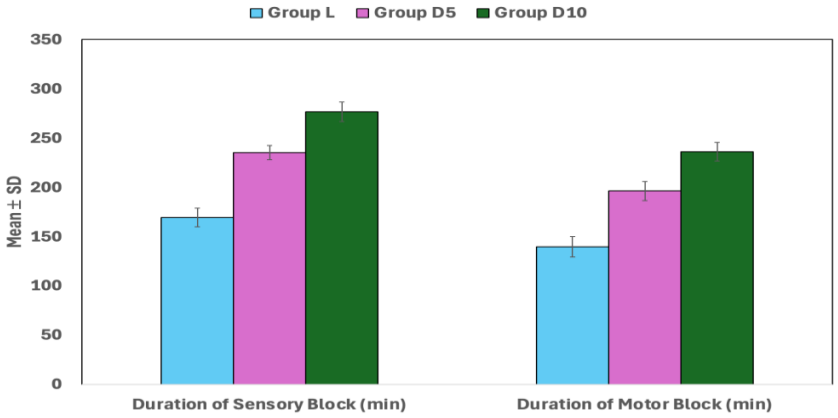

Figure 5: Bar diagram depicting intergroup comparison Duration of Motor & Sensory Block

The mean duration of motor block of group D10 was maximum (236.25 ± 9.39 min) and in group D5 (196.25 ± 9.66min) and minimum in group L (139.50 ± 10.49 min). The significant difference was found in mean duration of motor block between the groups (p<0.001)

Table 10: Intergroup comparison of complications

SN	Complications	Group L		Group D5		Group D10		Chi - sq test	
		No	%	No	%	No	%	$\chi 2$	'p'
1	Bradycardia	0	0.0	0	0.0	7	17.5	14.867	<0.001
2	Hypotension	0	0.0	0	0.0	5	12.5	10.434	<0.001

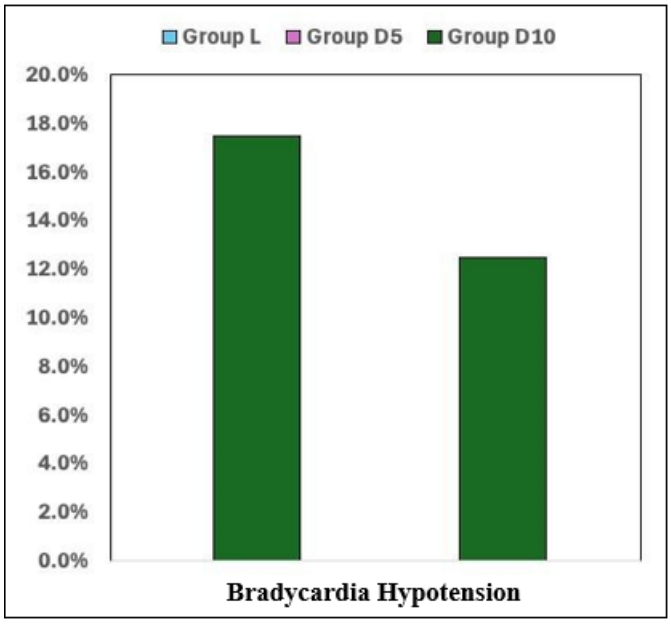

Figure 6: Bar diagram depicting intergroup of complications

None of the patients in Group L or Group D5 reported bradycardia or hypotension.17.5% of patients in Group D10 reported bradycardia and 12.5% reported hypotension. On comparing statistically, this difference was significant ($p<0.001$).

4. Discussion

The age of the patients ranged between 18 to 60 years (Mean age: 33.30 ± 8.17 years). Majority of the patients were aged between 21 to 40 years (79.2%). On comparing the age, gender and ASA grade between the groups, no significant difference was found among the groups

Heart - rate at 0 minute interval was comparable among the groups, however from 5 to 120 mins the heart - rate was higher at all intervals and statistically significantly higher at 5, 10 and 15 min in Group L and Group D5 as compared to Group D10. Hence, higher dose of dexmedetomidine (10 mcg) contributed to better heart rate control as compared to lower dose (5mcg) of dexmedetomidine and levobupivacaine heavy alone in a dose dependent manner.

Mean arterial pressure, at 0 minute interval was comparable among the groups. However, from 5 to 120 minutes, Group L and D5 exhibited higher mean arterial pressure at all intervals and statistically significantly higher at 5, 10 and 15 min in Group L and Group D5 as compared to Group D10. These results indicate that higher dose (10mcg) dexmedetomidine contributed to better mean arterial pressure control compared to lower dose (5mcg) of dexmedetomidine and levobupivacaine heavy alone. Similar findings were observed by **Songir et al. (2016)** [12] that the blood pressure was higher in control group, not receiving dexmedetomidine at all time intervals as compared to dexmedetomidine group. These results indicate that dexmedetomidine, particularly at the 10 mcg dose as compared to 5mcg dose, provided more stable intraoperative blood pressure control

Significantly earlier onset of sensory and motor block was achieved in Group D10 as compared to Group D5 and Group L. Further on between group comparison also, a significant difference was found between Group L vs. Group D5, Group L vs. Group D10 & Group D5 vs. Group D10 in terms of onset of motor and sensory block. In consistent with our findings **Saha et al. (2022)** [49] found that the maximum sensory level achieved was higher in Group D10 who received 10mcg of dexmedetomidine than in the other two groups (D5, D7.5) who received lower doses. There was a significant and dose - dependent shortening of the mean time to peak sensory block and peak motor block. **Kapinegowda *et al. (2017)*** [13] noted the onset time of sensory block being a dose dependent effect, as the dosage of dexmedetomidine increased the onset time of sensory block was significantly decreased. Similar findings were seen by **Gupta *et al. (2016)*** [11]**, Chattopadhyay et. al (2017)** [14] and **Shaikh & Dattatri et al. (2014)** [10]**,** all these studies elucidated a dose - response relationship between dexmedetomidine and intrathecal block characteristics, finding that higher doses resulted in earlier onset of sensory and motor blocks. The present study corroborates these findings, indicating that intrathecal 10 mcg dexmedetomidine offers superior efficacy in sensory and motor block onset as compared to 5mcg dexmedetomidine as an adjuvant to levobupivacaine heavy. These findings underscore the dose - dependent efficacy of dexmedetomidine in facilitating quicker block onset, which is advantageous in surgical settings requiring rapid anaesthesia onset

A significantly longer duration of sensory and motor block was achieved in Group D10 as compared to Group D5 and Group L. Further on between group comparison also, a significant difference was found between Group L vs. Group D5, Group L vs. Group D10 & Group D5 vs. Group D10 in terms of duration of motor and sensory block. Similar findings were observed by **Songir et al. (2016)** [12] that the blood pressure was higher in control group, not receiving dexmedetomidine at all time intervals as compared to dexmedetomidine group. These results indicate that dexmedetomidine, particularly at the 10 mcg dose as compared to 5mcg dose, provided more stable intraoperative blood pressure control. A significantly higher proportion of cases in Group D10 had bradycardia and hypotension as compared to Group D5 & Group L.

5. Conclusion

In our study depending on the data basis, we have concluded that the addition of adjuvant - like dexmedetomidine to hyperbaric levobupivacaine intrathecally produced a rapid onset of the sensory and motor blockade and prolonged duration of sensory and the motor block which was statistically significant in a dose - dependent manner.

We have also concluded that significant hypotension and bradycardia were noticed with the intrathecal use of 10 mcg as compared to 5mcg of intrathecal dexmedetomidine as an adjuvant to Levobupivacaine heavy. Use of 5mcg intrathecal dexmedetomidine as an adjuvant to Levobupivacaine heavy had minimal hemodynamic side effects in terms of managing patients undergoing infraumbilical surgeries.

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