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ORIGINAL RESEARCH

EVALUATE AND COMPARE INTRATHECAL PLAIN LEVOBUPIVACAINE AND DEXMEDETOMIDINE AS AN ADJUVANT TO 0.5% LEVOBUPIVACAINE FOR INFRA UMBILICAL SURGERIES

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ABSTRACT:
Background: Spinal anesthesia is a widely used technique providing faster onset with effective and uniformly distributed sensory and motor block. Due to decreased cardiovascular and central nervous system toxicity, levobupivacaine is a good alternative for spinal anesthesia.
Aim: The aim of this study is to evaluate and compare intrathecal plain levobupivacaine and Dexmedetomidine as an adjuvant to 0.5% Levobupivacaine for infra umbilical surgeries with respect to sensory and motor blockade, hemodynamic changes, and adverse effects.
Materials and methods: This is a prospective, randomized double blinded study conducted among 60 patients who were posted under elective infra-umbilical surgery. They were equally divided into Group L: They received intrathecal 0.5% Levobupivacaine 3cc Group LD: They received intrathecal 3 mcg dexmedetomidine with 0.5% Levobupivacaine.
Results: The addition of dexmedetomidine significantly prolonged the duration of sensory and motor block. The addition of dexmedetomidine significantly prolonged the time for rescue analgesia. The addition of intrathecal dexmedetomidine lead to an early onset of sensory block. The incidence of side effects was limited to the occurrence of hypotension and bradycardia in the group that received dexmedetomidine intrathecally.
Conclusion: Intrathecal dexmedetomidine as an adjuvant to spinal anaesthesia is good choice since it produces prolonged sensory and motor block.
Keywords: levobupivacaine, Dexmedetomidine, infra umbilical surgeries

INTRODUCTION:

Intrathecal anaesthesia and epidural anaesthesia are the most popular regional anaesthetic techniques used for lower abdominal & lower limb surgeries. Regional anaesthesia forms an excellent alternative due to its various advantages over general anaesthesia. Spinal anaesthesia is the most commonly used technique for infra umbilical surgeries because of easier administration ,lesser morbidity, effective postoperative analgesia and better hemodynamic profile intraoperatively .The properties of an anaesthetic agent used for day care surgeries in spinal anaesthesia should have decreased incidence of anaesthesia related complications, should provide adequate postoperative analgesia and allow early patient discharge. [1]

Among the amide local anaesthetics used in regional anaesthetic techniques bupivacaine has emerged as the most commonly used drug for central neuraxial blockade. Since then bupivacaine is extensively used and has become very popular for epidural anaesthesia as well as analgesia because of its long duration of action. Despite its undoubted efficacy, bupivacaine is associated with cardiotoxicity and neurotoxicity. Severe neurotoxic and cardiovascular adverse reactions reported in the literature after inadvertent intravascular injection or intravenous regional anaesthesia have been linked to the R(+) isomer of bupivacaine. The levorotatory isomers were shown to have a safer pharmacological profile with less cardiac and neurotoxic adverse effects.Apart from cardiotoxicity, it also carries undesirable effects like prolonged post operative motor blockade. Hence there was a need for introduction of drugs with all the features of bupivacaine but having less toxicity profile.[9]

The quest for searching newer and safer anaesthetic agents has always been one of the primary needs in anaesthesiology practice. Regional anaesthesia techniques have seen numerous modifications over the last two decades with the advent of many newer and safer local anaesthetics .[2,3,4]

Keeping these factors in mind, levobupivacaine has been developed. The advantages of levobupivacaine over bupivacaine are decreased cardiovascular toxicity and there is also a relatively decreased motor nerve fibre penetration and block, thereby a decreased post operative motor blockade and thus early ambulation of the patients can be achieved.

It demonstrated less affinity and strength of depressant effects onto myocardial and central nervous vital centres in pharmacodynamic studies and a superior pharmacokinetic profile. Reports of toxicity with levobupivacaine are scarce and occasional toxic symptoms are usually reversible with minimal treatment with no fatal outcome. In anaesthesia and analgesia practice, levobupivacaine and bupivacaine produce comparable surgical sensory block but levobupivacaine has the advantage of producing less motor blockade.[3]

The low cardiovascular and neurological toxicity of levobupivacaine has led to its varied utility in regional anaesthetic techniques including subarachnoid block, epidural anaesthesia and analgesia, brachial plexus blocks as well as local infiltration. It is also being used for intraoperative anaesthesia, labour analgesia, and postoperative pain management. Both levobupivacaine and ropivacaine are being favoured in labour analgesia because of comparable long lasting analgesia, less motor block and less toxicity compared to bupivacaine.[5]

Efforts to find a better adjuvant in regional anaesthesia are underway since long. The addition of adjunctive agents (opioids & alpha 2 agonists) to local anaesthetics via epidural and intrathecal routes may provide a dose sparing effect and increase the duration and quality of analgesia.Opioids like fentanyl have been used traditionally as an adjunct for epidural administration in combination with lower dose of local anaesthetic to achieve the desired anaesthetic effect. The addition of opioid does provide a dose sparing effect of local anaesthetic and superior analgesia but there is always a possibility of an increased incidence of pruritis, urinary retention, nausea, vomiting and respiratory depression.The pharmacologic

properties of alpha 2 agonist have been extensively studied and have been employed clinically to achieve desired effects in regional anaesthesia. Clonidine is an alpha-2 adrenergic agonist which, when administered by epidural route, has analgesic properties and potentiates the effect of local anaesthetics. Clonidine is 200-folds more selective for alpha-2 as compared to alpha-1.

Dexmedetomidine, made up of medetomidine‟sdextrogyrousenantiomer,is currently considered a super selective alpha-2 adrenergic agonist prototype and is 1600-folds more selective for alpha-2 receptor. Dexmedetomidine is a highly selective alpha 2 adrenergic agonist with greater receptor affinity than clonidine.[4]Hence the present study is to evaluate the effects of addition of dexmedetomidine to intrathecal 0.5% levobupivacaine in infra-umbilical surgeries.

METHODS AND METHODOLOGY:

Randomised Control Study in 60 patients belonging to ASA grade I and II were studied during a period of 1 year , i.e. between November 2019- November 2020 in Gandhi Medical Hospital.

INCLUSION CRITERIA:

After taking informed and written consent, 60 patients between the age groups of 18 and 60 years of age belonging to ASA grade I and II having ±20% of ideal body weight posted electively for infra umbilical surgeries under spinal anaesthesia were taken up for the study.

EXCLUSION CRITERIA:

Allergy to any of the drugs, Coagulationdisorders/Bleedingdisorders, Infection at the site of block, Patients with spine injury or h/o spine surgery and pregnantandlactatingwomen.

After obtaining institutional ethical committee approval and by applying inclusion and exclusion criteria, 60 Patients were entered in to the study. Every patient was explained in their own language about the purpose and conducting method of the study and an informed written consent was obtained. The documentation was strictly included a detailed history, complete physical examination and investigations such as hemoglobin, blood sugar, renal function parameters, ECG for all patients. Each patient was randomized into either group by computer randomization.

Data was collected in pretested pro forma meeting the objectives of the study. All patients were premedicated on the night before surgery with tablet ranitidine 150mg, fasted 8 hours for solid food and 4 hours for clear fluids. Intravenous line was secured with 18 gauge cannula on the forearm /wrist ,the patient was preloaded with 10ml/kg of ringer lactate, half an hour before anaesthesia. All patients received Inj. ranitidine and Inj. midazolam IV according to their weight , 30 minutes before surgery. Baseline reading of vital parameters was checked in the waiting room.

In the operating room, anaesthetic machine, equipments for airway management and emergency drugs were kept ready. Horizontal position of operating table was checked. Patient was connected to electrocardiography (ECG), Non-Invasive Blood Pressure (NIBP) and arterial pulse saturation (SPO2) monitor. Preoperative heart rate, systolic and diastolic blood pressure, mean arterial pressure and oxygen saturation were recorded. Patients were placed in sitting position. Under aseptic precautions lumbar puncture was performed at the level of L2-L3 or L3-L4 through a midline approach using 25 G Quincke‟s spinal needle and study drug was injected after confirmation of needle tip in the subarachnoid space by clear and free flow of Cerebrospinal Fluid.

Group LD: 0.5% Isobaric Levobupivacaine 15mg (3ml) + Dexmedetomidine 3µg (0.3ml).

Group L: 0.5% Isobaric Levobupivacaine 15mg (3ml) + Normal saline (0.3ml).

Dexmedetomidine for intrathecal use was prepared by diluting 0.5 ml of drug containing 50 μg to 4.5 ml of normal saline. 0.3 ml of this diluted solution (containing 3 μg) was taken and added to syringe containing 3ml of 0.5% isobaric levobupivacaine . Spinal anaesthesia was performed and the data were collected using prescribed pro-forma. Patient was made to lie down in the supine posture immediately with the table kept flat horizontally and supplemental oxygen was given. The time at which spinal anaesthesia performed was noted.

The following parameters were observed and recorded as Onset of motor blockade., Time to complete motor blockade, Onsetofsensoryblockade, Maximum level of sensory blockade attained and the time taken for the same, Time for two segments sensory regression, Any discomfort like nausea, vomiting, shivering and adverse events such as hypotension, bradycardia, and ECG changes were noted and Postoperative pain were assessed using Visual analogue scale (0 – 10) at 30 minutes, hourly for the next 5 hours and time to first rescue analgesic request was recorded.

On completion of surgery, patient was shifted to post operative ward for observation. Vital signs and oxygen saturation were monitored until recovery of patients from anaesthesia. Injection diclofenac sodium 75mg was given IM when the patient complained of pain in the postoperative period (VAS >3) as Rescue analgesic and time was noted.

Hypotension was said to have occurred if Systolic blood pressure decreased less than 100 mm of Hg or if Diastolic blood pressure decreased less than 50 mm of Hg or if the MAP decreased less than 60 mm of Hg. Patient was treated with 100% O2, increasing the infusion rate of IV fluids and Inj. Mephentermine 6mg bolus . Bradycardia was defined as heart rate less than 60/min and was treated with intravenous atropine 0.6mg IV.

Sensory block The onset of sensory block was defined as the time between the injection of anaesthetic solution and loss of sensation at the T6 dermatome. Sensory block was assessed by loss of sensation to pinprick with a 22G hypodermic needle along midclavicular line bilaterally .This assessment started immediately after turning the patient to supine position and continued every minute till loss of sensation to pinprick at T6 level was noted. Maximum level of sensory blockade and time taken for the same: was defined as the time from the injection of the anaesthetic solution to the maximum level of sensory blockade attained. The duration of sensory block was defined as the time between the intrathecal administration of anaesthetic solution and two segment sensory regression.

Duration of two segment sensory regression: was defined as the time taken from the maximum level of sensory block attained till the sensation has regressed by Two segments.

Motor block(MB) Motor block was assessed bilaterally using Modified Bromage scale.

MODIFIED BROMAGE SCORE:

0 - Able to move the hip, knee and ankle.

1 - Unable to move the hip, but able to move knee and ankle (onset).

2 - Unable to move the hip and knee, but able to move the ankle.

3 - Unable to move the hip, knee and ankle (maximum).

Assessment of motor block was started immediately after turning the patient to supine position and continued every minute till Bromage score of 3 was reached which defines maximum motor block and time to achieve it was noted.

The onset of motor block was defined as the time to achieve Bromage score of 1 from the time of intrathecal injection. Total Duration of Analgesia was defined as the time taken from onset of sensory block to VAS greater or equal to 1.

RESULTS :

All 60 patients with ASA physical status I/II who satisfied all inclusion criteria were randomly divided into two groups and underwent elective infra umbilical surgeries under subarachnoid block in Gandhi Medical Hospital, Secunderabad.All the patients completed the study without any exclusion.

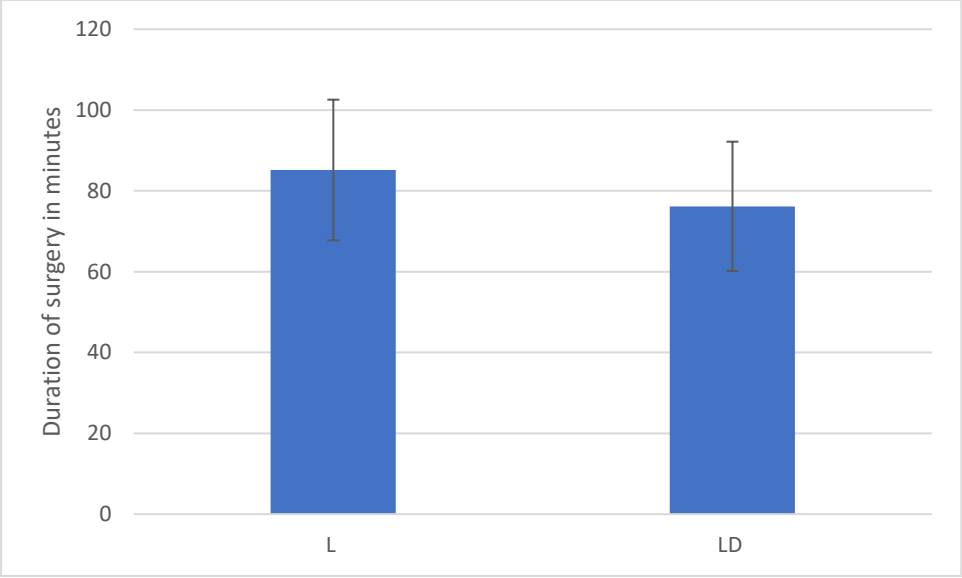
The collected data were analyzed by t test and results obtained in form of mean and standard deviation. The probability value $p < 0.05$ is considered as statistically significant. The results were as follows:

Table 1: Demographic Distribution between the groups .

Variables			Group		Total
			L	LD	
Sex	Female	Count	10	11	21
		%	33.3%	36.7%	35.0%
	Male	Count	20	19	39
		%	66.7%	63.3%	65.0%
Total		Count	30	30	60
		%	100.0%	100.0%	100.0%
Age in years(mean +SD)			43.33+12.75	40.83+14.06	.474
ASA	I	Count	18	15	33
		%	60.0%	50.0%	55.0%
	II	Count	12	15	27
		%	40.0%	50.0%	45.0%

Demographic variables are non significant in gender, age and ASA.

Figure-1: Duration of surgery between the groups .



Duration of surgery is non significant when compared in both groups.

Table-2: Maximum sensory block level between the groups

			Group		Total
			L	LD	
Max.Sensory Block Level	T10	Count	0	4	4
		%	0.0%	13.3%	6.7%
	T8	Count	20	17	37
		%	66.7%	56.7%	61.7%
	T6	Count	10	9	19
		%	33.3%	30.0%	31.7%
Total		Count	30	30	60
		%	100.0%	100.0%	100.0%
CHI SQUARE = 4.296, P VALUE = 0.117 (Not significant)					

Maximum sensory block level between the groups are insignificant.

Table-3: Sensory block parameters in present study

Variable	Group	Mean	Std. Deviation	P VALUE
Onset Of Sensory Block (T10)	L	3.383	1.0313	.014
	LD	2.800	.7144	
Time To Max Sensory Level	L	9.683	1.1179	.003
	LD	8.817	1.0626	
Time For Regression To T10	L	85.050	4.7112	.001
	LD	97.867	4.1062	
Total Duration Of Sensory Block	L	181.700	4.3700	.001
	LD	292.650	20.8348	

Onset of sensory block, time to max sensory level, time for regression is significantly high in Group -L when compared to Group-LD.

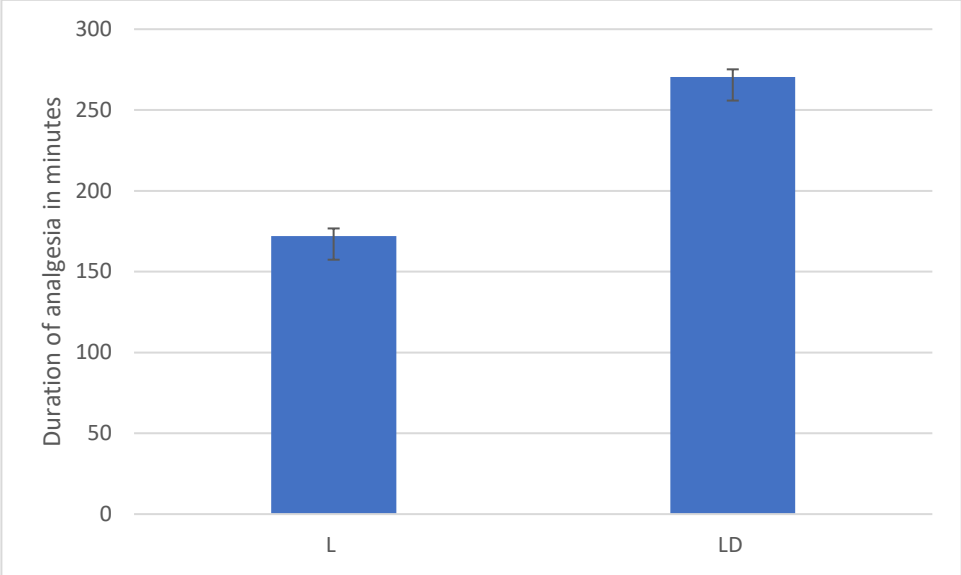
T10 and total duration of sensory block is significantly low in Group -L when compared to Group-LD.

Table-4: Comparing the variables of motor block between the two groups

Variable	Group	Mean	Std. Deviation	P VALUE
Onset for Motor Block	L	3.90	.960	.656
	LD	3.80	.761	
Time for Max Motor Block	L	10.817	1.8075	.669
	LD	10.983	1.1179	
Total Duration of Motor Block	L	149.850	3.3506	.001
	LD	192.400	19.0654	

Total Duration of Motor Block is significantly low in Group -L when compared to Group-LD. Onset for Motor Block and Time for Max Motor Block are insignificant.

Figure-2: Duration of analgesia in present study in both groups



Duration of analgesia is significantly less in Group -L when compared to Group-LD.

Table-5: Comparing the need for Rescue analgesia between the two groups

			Group		Total
			L	LD	
Rescue analgesia	NO	Count	25	29	54
		%	83.3%	96.7%	90.0%
	YES	Count	5	1	6
		%	16.7%	3.3%	10.0%
Total		Count	30	30	60
		%	100.0%	100.0%	100.0%
CHI SQUARE = 2.963, P VALUE = 0.04 (S)					

There is no need rescue analgesia Group -LD when compared to Group-L between the two groups.

Table-6: Side effects between the two groups

			Group		Total
			L	LD	
Hypotension	NO	Count	27	25	52
		%	90.0%	83.3%	86.7%
	YES	Count	3	5	8
		%	10.0%	16.7%	13.3%
CHI SQUARE = 0.577, P VALUE = 0.448 (NS)					
Bradycardia	NO	Count	30	24	54
		%	100.0%	80.0%	90.0%
	YES	Count	0	6	6
		%	0.0%	20.0%	10.0%
CHI SQUARE = 6.667, P VALUE = 0.010 (S)					
Nausea /Vomiting	NO	Count	28	27	55
		%	93.3%	90.0%	91.7%

YES	Count	2	3	5
	%	6.7%	10.0%	8.3%

CHI SQUARE = 0.218, P VALUE = 0.640 (NS)

Bradycardia is significantly less number of patients in Group -L than in Group-LD. Hypotension, nausea and vomiting are insignificant when compared in both groups.

Table-7: Comparison of Post Operative VAS scores between the two groups

	Group	Mean	Std. Deviation	P VALUE
VAS 0 min	L	.00	.00	--
	LD	.00	.00	
VAS 30 min	L	.00	.00	--
	LD	.00	.00	
VAS 1hr	L	.00	.00	--
	LD	.00	.00	
VAS 2hr	L	1.47	1.383	.001
	LD	.00	.00	
VAS 3hr	L	2.20	.805	.001
	LD	.00	.00	
VAS 4hr	L	2.57	.728	.001
	LD	1.07	1.015	
VAS 5hr	L	3.23	.626	.001
	LD	2.10	.845	

Post Operative VAS scores between the two groups is significantly high in Group L when compared to Group-LD.

DISCUSSION:

Regional anaesthesia is the most widely technique for infra umbilical surgeries. It is preferred over general anaesthesia because general anaesthesia is associated with increased respiratory complications and postoperative morbidity comparatively. Incidence of high regional block and local anaesthetic toxicity are the causes of mortality with regional technique.Due to improved monitoring equipments and less cardiotoxic drugs in clinical practices ,local anaesthetic systemic toxicities has also been reduced nowadays.

Varying techniques and drug regimens were used over years to improve the quality of spinal anaesthesia. α-2-adrenoceptor agonists are being currently explored in anaesthetic field for their sedative, analgesic, sympatholytic, anaesthetic-sparing and favourable haemodynamic properties. Dexmedetomidine, is one such agonist having a relatively high α_2/α_1-activity ratio (1620:1) as compared to clonidine (220:1). It‟s also unique that it lacks respiratory depressant action, and conscious sedation making it therapeutically a useful and safe adjunct. Levobupivacaine was used as a local anaesthetic because it produces faster onset of anaesthesia and prolonged postoperative analgesia. It causes less density in motor blockade than bupivacaine and also lesser side effects like cardiotoxicity.

In this study, we observed that adding dexmedetomidine to Levobupivacaine prolonged the sensory and motor block duration in patients posted for infra umbilical surgeries under spinal anaesthesia. Clonidine, an intrathecal α_2 adrenoceptor agonist, has been used intrathecally in many studies which provided adequate clinical experience about the agent; studies focusing on intrathecal use of dexmedetomidine and its combined use with local anaesthetics are not sufficient.Although dexmedetomidine has been approved by the Food and Drug

Administration as a sedative for mechanically-ventilated adult intensive care unit patients, it has not been approved for intrathecal use. However, dexmedetomidine used in neuraxial blocks in experimental and clinical studies without neurological deficits has encouraged the use of dexmedetomidine by the intrathecal route with Levobupivacaine[6]To the best of our knowledge, this combination has not been used previously by the intrathecal route in humans, which shows the importance of this study. The intrathecal application of dexmedetomidine in the 2.5–100 μg dose range has been investigated in rats, rabbits, dogs, and sheep A 100 μg dose of intrathecal dexmedetomidine was employed in sheep but no neurological deficit was observed during a follow-up period of 7 days. Calasans- Maia et al.[7]investigated the effects of adding intrathecal or intraperitoneal dexmedetomidine to 0.5% levobupivacaine over motor block duration in pigs and found that both intrathecal dexmedetomidine (0.1, 0.2, and 0.4 μg) and intraperitoneal dexmedetomidine (20 and 40 μg/kg) prolonged the motor block duration.

In our study, both groups were comparable with respect to demographic profile, duration and type of surgery. The primary outcome of the present study was early onset and increased duration of sensory block and motor block along with prolong postoperative analgesia. In the present study, among group L, the mean time of onset of sensory block was 3.383±1.03 minutes and mean time of onset of motor block was 3.90±0.96 minutes. Among group LD, the mean time of onset of sensory block was 2.8±0.71 minutes and mean time of onset of motor block was 3.80±0.76 minutes. The association between the differences in mean time of onset of sensory block was statistically significant and motor block of both the study groups was not statistically significant with P value of >0.05.

Table-8: The findings of the present study are comparable with the following studies:

Author	Group L	Group LD	P value
onset of sensory block			
Present study	3.383±1.03 minutes	2.8±0.71 minutes	0.14
Amar kataria et al.[6]	7.56 ±1.52minutes	4.90 ±0.88 minutes	<0.001
Sinitipatro etal.[8]	208.33±19.18 seconds	129.33±14.84 seconds	<0.001
Motor component			
Present study	3.90±0.96 minutes.	3.80±0.76 minutes.	0.656
Amar kataria et al.[6]	3.0±0.62 minutes.	3.47±0.776 minutes.	>0.05
Sinitipatro etal.[8]	320.33±29.81seconds	226±31.86 seconds	<0.05
Duration of analgesia			
Present study	181.7 ± 4.37 min	292.65 ± 20.83 min	0.001
Amar kataria et al.[6]	199.50±7.76min	340.20± 11.78 min	<0.001
Sinitipatro etal.[8]	188±11.86 min	317.7±16.16 min	<0.001
Kazani et al.[9]	190± 44.6min	303± 23.3 min	<0.0001
mean duration of motor block			
Present study	149.85± 3.35 min	192.40± 19.06 min	<0.001
Amar kataria et al.[6]	150.83± 9.17min	190.20± 9.61 min	<0.001

In the present study, the duration of analgesia in group L was 181.7± 4.37 minutes. The duration of analgesia among group LD was 292.65 ± 20.83 minutes. The difference between the two means was statistically significant with P value of 0.001. In the present study, the mean duration of motor block in group L was 149.85 min and among group LD was 192.4minutes. The difference between the two was statistically significant with P value of <0.001. In the present study, among group L, 16.7% needed doses of analgesics. Among group LD, 3.3% needed doses of analgesics, with a p value of 0.04. The addition of

dexmedetomidine to levobupivacaine improved the postoperative analgesia resulting in a reduction of the number of analgesic doses required in the 24 h postoperatively. Better degree of analgesia in Group LD seen in our study was due to the synergism of dexmedetomidine and levobupivacaine and effectiveness of dexmedetomidine in abolishing visceral pain. This was in accordance with studies conducted by Kim et al.[10]Basuni[11] and Eid et al.,[12] and Ameret al[13]. Hypotension was seen in 10% of patients in Group L and 16.7% Group LD and bradycardia was 0 in Group L and 20% in Group LD, and the differences were statistically nonsignificant (P > 0.05) between the two groups (P > 0.05) as observed byAmeretal[13] reported that the addition of clonidine to bupivacaine in spinal anaesthesia prolonged block duration, but decreased the mean blood pressure and heart rate significantly compared with the control group. Kanazi et al.[9] noted that dexmedetomidine or clonidine added to intrathecal bupivacaine did not cause a significant reduction in blood pressure. In the study of Gupta et al.[14] hypotension was more severe in the dexmedetomidine group than in the fentanyl group, but no statistically significant difference was determined between the groups. In this study, we observed theoccurrence of bradycardia was seen only in the LD group with 6 patients. The resultant p value was 0.010 which was statistically significant. The occurrence of post operative nausea and vomiting between both the groups was not statistically significant (p value 0.640).

In conclusion, the combined use of 3 μg dexmedetomidine and levobupivacaine in spinal anaesthesia prolongs sensory and motor block durations without causing any significant side effects.

CONCLUSION:

Intrathecal dexmedetomidine as an adjuvant to spinal anaesthesia seems to be a good choice since it produces prolonged sensory and motor block. There is an early onset of sensory block and longer duration of analgesia in the postoperative period which leads to fewer doses of rescue analgesia. Low dose of Dexmedetomidine is associated with less hemodynamic variations intra operatively, it is evident that this type of block is more suitable for lower abdomen and lower extremities surgeries.

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