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Original Research Article

A Prospective Observational Study to Evaluate the Efficacy and Adverse Effects of Levobupivacaine in Combination with Fentanyl during Lower Abdominal Surgeries under Spinal Anaesthesia

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Abstract: Spinal anaesthesia is a popular and commonly used technique for lower abdominal surgeries. The aim of our study to evaluate the efficacy and adverse effects of levobupivacaine in combination with fentanyl during lower abdominal surgeries under spinal anaesthesia. After taking due consent from 50 patients of either sex, aged between 18 - 60 years, American Society of Anaesthesiologists (ASA) physical status Grade I and II, we have designed a prospective double- blinded randomised study which is to be performed in Teerthanker Mahaveer medical college and Research Center, undergoing elective lower abdominal surgeries (viz. urological and general surgical procedures) under spinal anaesthesia. In this study, intrathecal administration of injection levobupivacaine 0.5% (2.5 ml) + fentanyl 25 µg (0.5 ml) was given. Post-Hoc Bonferroni test was used to compare SBP, DBP, PR and HR between diffrent time intervals. The above mentioned parameters result were statically significant. Duration of surgery, Sensory block (Time to achieve height of T10, Maximum height of block and time to two segment regression), Motor block (Time to modified Bromage score and Time to complete block) were found to be statistically insignificant. Levobupivacaine when combined with Fentanyl provided better surgical anaesthesia and hemodynamic stability for lower abdominal surgeries.
Keywords: Fentanyl, Levobupivacaine, Spinal Anaesthesia.

INTRODUCTION

Spinal anaesthesia is a popular and commonly used technique for lower abdominal surgeries. The advantages of an awake patient, minimal drug costs and rapid patient turnover has made subarachnoid block as the method of choice for many surgical procedures [1]. However, spinal anaesthesia for supraumblical/ paraumbilical surgeries is more complicated; as higher level of sensory block is required [2]. Increasing the dose of long-acting local anaesthetics for such special cases may produce extensive sensory and motor block as well as arterial hypotension and this result in delayed discharge from hospital [3].

Levobupivacaine (S enantiomer of racemic bupivacaine) is a local anaesthetic having similar efficacy but an enhanced safety profile when compared to bupivacaine, a major advantage in regional anaesthesia [2, 3]. On comparison with bupivacaine, levobupivacaine is associated with less vasodilation and has longer duration of action [4].

Fentanyl (µ-opioid receptor agonist) is a lipophilic opioid has rapid onset of action following intrathecal administration. It proves to be a safer alternative than morphine as it does not migrate to the fourth ventricle in sufficient concentration to cause delayed respiratory depression when administered intrathecally [5]. Moreover, intrathecal opioids added to local anaesthetics enhance analgesia without intensifying motor and sympathetic block, and make it possible to achieve successful anaesthesia in spite of the use of a low dose local anaesthesia [4,5].

Considering promising advantageous roles of levobupivacaine with fentanyl in spinal anaesthesia, our aim is to compare the efficacy and side effects of levobupivacaine in combination with fentanyl during lower abdominal surgeries under spinal anaesthesia.

MATERIALS AND METHODS

After Institutional Ethical Approval and taking due consent we designed a prospective randomised double- blinded study in Department of Anaesthesia, Teerththanker Mahaveer medical college and Research Centre. Sixty patients of either sex, aged between 18 - 60 years, American Society of Anaesthesiologists (ASA) physical status Grade I and II, undergoing elective lower abdominal surgeries (viz. urological and general surgical procedures) under spinal anaesthesia were included in the study.

All patients not giving consent, prior history of spine surgery, infection at the injection site, coagulopathy, hypovolemia, increased intracranial pressure, indeterminate neurologic disease, spinal deformities, communication problems, known hypersensitivity to local anaesthetics and opioids were excluded from the study.

In this study, intrathecal administration of injection levobupivacaine 0.5% (2.5 ml) + fentanyl 25 µg (0.5 ml) was given. Intrathecal drugs were prepared by an independent anaesthesiologist not involved in the study and the drug mixture to be administered by another anaesthesiologist who was blinded and performing spinal anaesthesia. Volume of the drug, size of the syringe and colour of the drug of interest was similar in both groups.

All patients were premedicated with Inj. Ondanstetron (4 mg IV) and preloading was done by Lactate Ringer’s (10 ml per kg). Standard monitors were attached. Spinal anaesthesia was performed in all patients in the sitting position. Under strict aseptic precautions, using 25G Quincke needle, spinal needle was introduced at L3-L4 level. After confirming free flow of cerebrospinal fluid, a total volume of 3 ml of spinal solution was administerd into the intrathecal space in each patient over approxiamately 10-15 seconds. Patients were moved to the supine position immediately after administering the spinal block. The completion of the injection was taken as zero time of the induction of anaesthesia.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) was recorded every 3 min up to 30 min and then every 15 min up to 90 min irrespective of the duration of surgery. Hypotension is defined as SBP <90 mm Hg or >30% fall from the baseline value and was treated by Inj. Mephentermine (6 mg IV) and an additional bolus of 100 ml of Ringer lactate. Bradycardia was defined as HR <50 beats/min or >30% decrease from the baseline value and was treated with Inj. Atropine (0.5 mg IV).

Sensory block level, defined as the loss of pain sensation to pin prick test in the mid-clavicular line, was measured every 1 min and the surgery was allowed to proceed when T10 block level was achieved. Peak sensory block level (PSBL) was assessed every 2 minutes and defined as the level that remained same during four consecutive tests. Time to reach peak block level was also noted. The time to two segment regression (TTSR) was noted by checking every 10 min after the peak block level was reached.

The degree of motor blockade at the time of peak sensory block was assessed using a Modified Bromage scale [6].

The quality of anaesthesia was assessed as excellent (no discomfort or pain), good (mild pain or discomfort and no need for additional analgesics), fair (pain that required non-opioid analgesics), poor (severe pain that required opioids). Inj. Diclofenac sodium (1-1.5 mg/kg IM) was administered on request as rescue analgesic. Side- effects such as hypotension, bradycardia, pruritus, and vomiting, respiratory depression was monitored and managed accordingly.

Statistical analysis

A sample size calculation was performed using the standard deviation of the time to the first request for analgesics. To detect a 30 min difference in the mean duration of the first request for analgesics (two sided-alpha of 5% and beta of 10%), 23 subjects was required. After factoring in attrition rate of 10%, the final sample size was taken 50.

Statistical analysis was performed using Statistical package for social sciences (SPSS) for Windows version 19.0 software, Chicago, SPSS Inc. Student *t*-test was used to analyse age, weight, height, pulse rate, SBP, DBP, time to T10 block, time to PSBL, TTSR. Chi- square was used to analyse PSBL, maximum motor blockade and side- effects. A $P < 0.05$ was considered as statistically significant.

RESULTS

Demographic data

In the present study undertaken, out of the 50 patients undergoing for lower abdominal surgeries 39 (78%) were male and rest 11(22%) were females [Table 1, Figure 1].

The mean age for the Male was 40.28±13.28, females were 38.09±9.93 and for the over-all population was 39.80±12.43. [Table 2]

Table-1: Gender distribution data

Sex	Frequency	Percent
Female	11	22.0
Male	39	78.0
Total	50	100.0

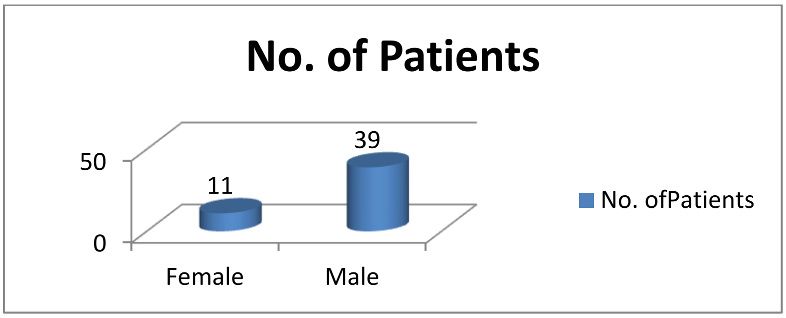

Fig-1: Gender distribution data

Table-2: Age distribution data

	Age		
Sex	**Number**	**Mean**	**Std. Deviation**
Male	39	40.28	13.28
Female	11	38.09	9.93
Over-all	50	39.80	12.43

Table-3: Basal Metabolic Index data

	Minimum	Maximum	1st Quartile	Median	3rd Quartile	Mean	Standard deviation
Age	12.00	58.00	30.50	43.00	50.00	39.80	12.43
Height	145.00	175.00	160.25	165.50	171.00	165.06	7.07
Weight	45.00	82.00	60.25	65.00	73.50	66.16	8.47
BMI	20.00	31.00	22.00	24.00	26.00	24.13	2.47

Hemodynamic Parameters

The comparison of mean PR was done between different time intervals using the **Repeated measures ANOVA test**. There was a significant difference in mean PR between different time intervals. [Table 4, Fig 2].

The inter-group comparison of mean PR was done between different time intervals using the **Post-hoc bonferroni test**. The mean PR was significantly more at after spinal injection and 3 minutes in comparison to Pre-operatively, 9 minutes, 15 minutes, 45 minutes and 60 minutes. The mean PR was significantly more at 3 minutes in comparison to 9 minutes.

Table-4: Pulse rate data

	PR	Mean	Std. Deviation	F-value	p-value[a]	Post-hoc comparisons[b]
1.	**Pre-operatively**	88.08	4.17	14,879.251	< 0.001*	2, 3 > 1, 5, 6, 8, 9 3 > 4
2.	**After spinal injection**	92.16	5.65			
3.	**3 minutes**	91.84	4.71			
4.	**6 minutes**	89.60	4.34			
5.	**9 minutes**	87.68	5.14			
6.	**15 minutes**	87.16	4.70			
7.	**30 minutes**	86.48	10.18			
8.	**45 minutes**	87.32	3.54			
9.	**60 minutes**	87.36	4.10			
10.	**75 minutes**	87.84	3.65			
11.	**90 minutes**	85.92	10.14			

[a] **Repeated measures ANOVA test**
[b] **Post-hoc bonferroni test**
*** Significant difference**

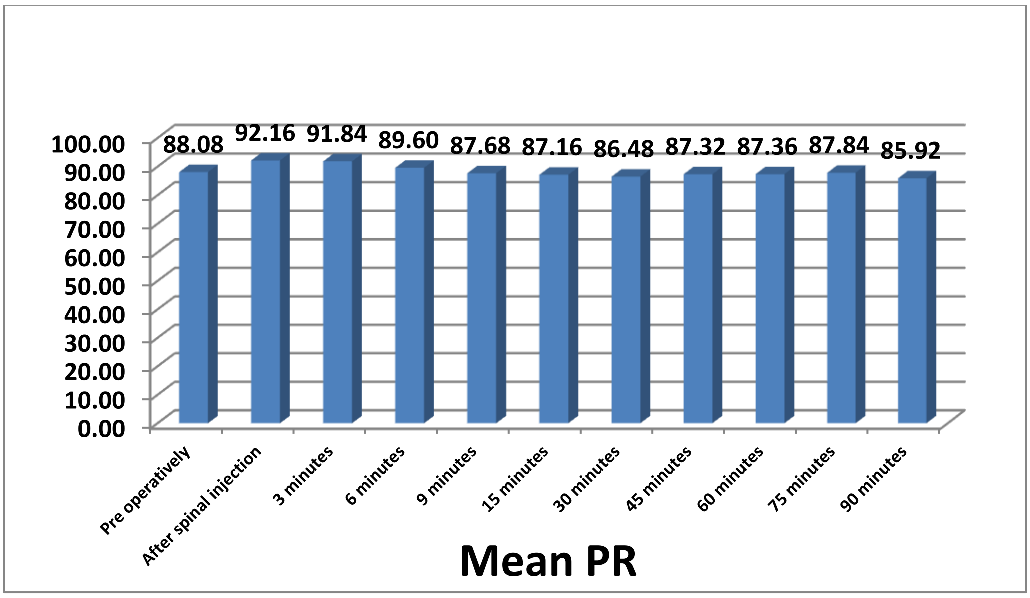

Fig-2: Mean PR

The comparison of mean SBP was done between different time intervals using the **Repeated measures ANOVA test**. There was a significant difference in mean SBP between different time intervals.[Table 5, Fig 3]

The inter-group comparison of mean SBP was done between different time intervals using the **Post-hoc bonferroni test**. The mean SBP was significantly more at Pre-operatively in comparison to at 90 minutes which was significantly more than at 45, 60 and 75 minutes which was significantly more than at 3 minutes, 6 minutes, 9 minutes, 15 minutes and 30 minutes.

Table-5: Systolic blood pressure data

	SBP	Mean	Std. Deviation	F-value	p-value[a]	Post-hoc comparisons[b]
1.	**Pre operatively**	127.92	8.03	17,711.502	< 0.001*	1 > 11 > 8, 9, 10 > 2, 3, 4, 5, 6, 7
2.	**After spinal injection**	114.00	5.74			
3.	**3 minutes**	113.68	4.50			
4.	**6 minutes**	116.08	4.09			
5.	**9 minutes**	117.20	4.73			
6.	**15 minutes**	118.40	5.72			
7.	**30 minutes**	119.28	6.57			
8.	**45 minutes**	122.64	5.59			
9.	**60 minutes**	121.84	5.06			
10.	**75 minutes**	121.92	6.07			
11.	**90 minutes**	124.32	7.34			

[a] **Repeated measures ANOVA test**
[b] **Post-hoc bonferroni test**
*** Significant difference**

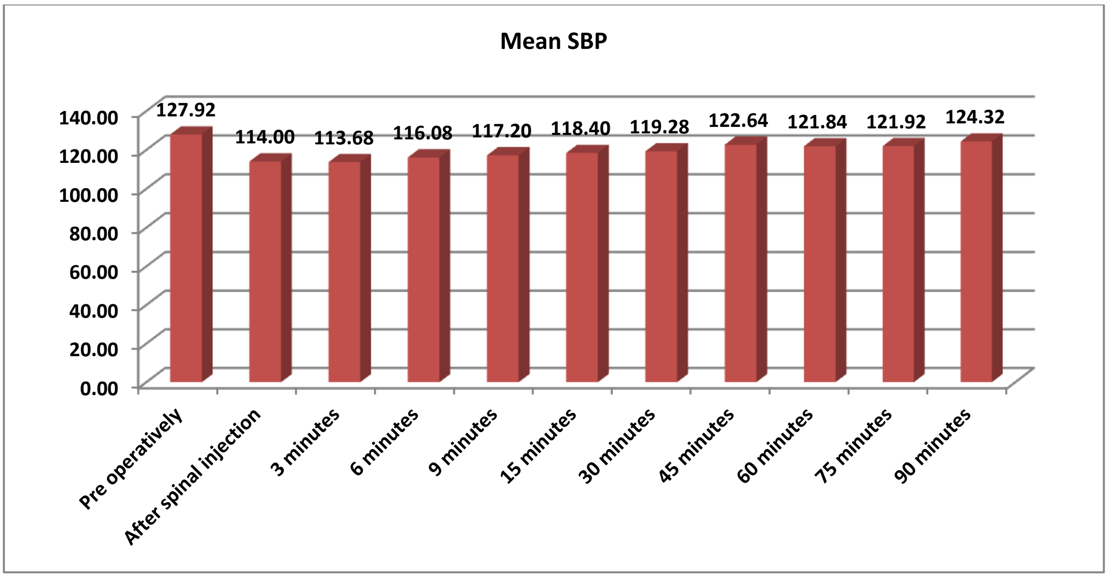

Fig-3: Mean SBP

The comparison of mean DBP was done between different time intervals using the **Repeated measures ANOVA test**. There was a significant difference in mean DBP between different time intervals. [Table 6,Fig 4]

Table-6: Diastolic blood pressure data

	DBP	Mean	Std. Deviation	F-value	p-value[a]	Post-hoc comparisons[b]
1.	**Pre operatively**	82.48	6.56	5,069.809	< 0.001*	1 > 5,6,7 8,9,10,11 > 5, 6 8,11 > 7
2.	**After spinal injection**	80.48	9.85			
3.	**3 minutes**	80.32	9.83			
4.	**6 minutes**	80.16	10.74			
5.	**9 minutes**	75.92	8.97			
6.	**15 minutes**	75.36	8.14			
7.	**30 minutes**	76.96	8.44			
8.	**45 minutes**	81.76	5.24			
9.	**60 minutes**	82.00	4.76			
10.	**75 minutes**	83.12	4.76			
11.	**90 minutes**	83.04	5.20			

[a] Repeated measures ANOVA test
[b] Post-hoc bonferroni test
*** Significant difference**

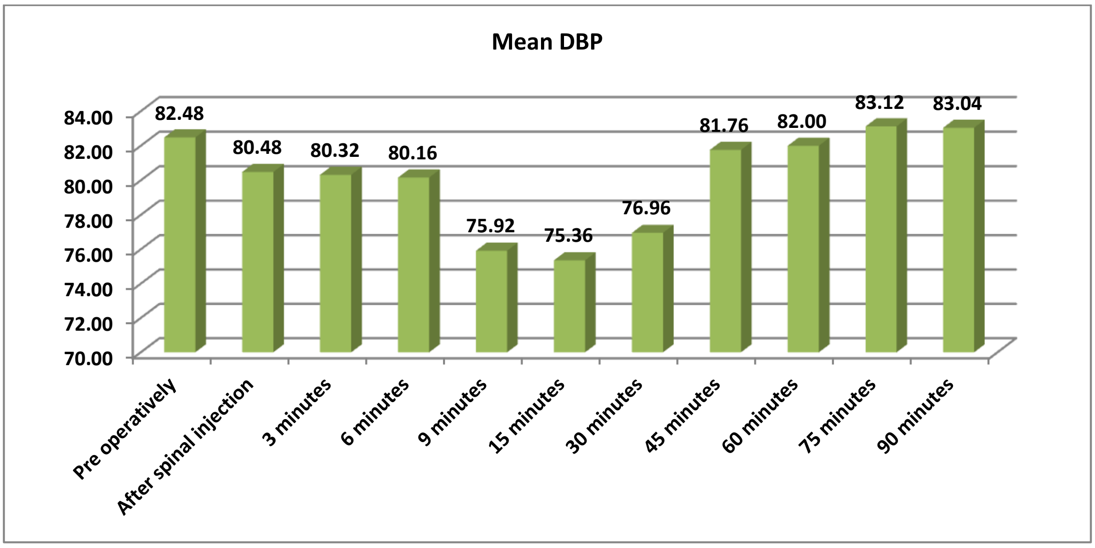

Fig-4: Mean DBP

The comparison of mean MAP was done between different time intervals using the **Repeated measures ANOVA test**. There was a significant difference in mean MAP between different time intervals.[Table 7, Fig 5]

The inter-group comparison of mean MAP was done between different time intervals using the **Post-hoc bonferroni test**. The mean MAP was significantly more pre-operatively in comparison to after spinal injection, at 3, 6, 9, 15 and 30 minutes. The mean MAP was significantly more at 45, 60, 75 and 90 minutes in comparison to 15 and 30 minutes.

Table-5: Mean arterial pressure data

	MAP	Mean	Std. Deviation	F-value	p-value[a]	Post-hoc comparisons[b]
1.	**Pre operatively**	98.67	7.80	8,753.913	< 0.001*	1 > 2,3,4,5,6,7 8,9,11 > 6, 7 8 > 3
2.	**After spinal injection**	91.13	6.37			
3.	**3 minutes**	90.67	6.75			
4.	**6 minutes**	91.58	7.51			
5.	**9 minutes**	89.42	7.90			
6.	**15 minutes**	89.25	7.11			
7.	**30 minutes**	90.46	7.29			
8.	**45 minutes**	95.17	4.96			
9.	**60 minutes**	95.50	4.64			
10.	**75 minutes**	95.54	4.99			
11.	**90 minutes**	96.54	5.91			

[a] Repeated measures ANOVA test
[b] Post-hoc bonferroni test
*** Significant difference**

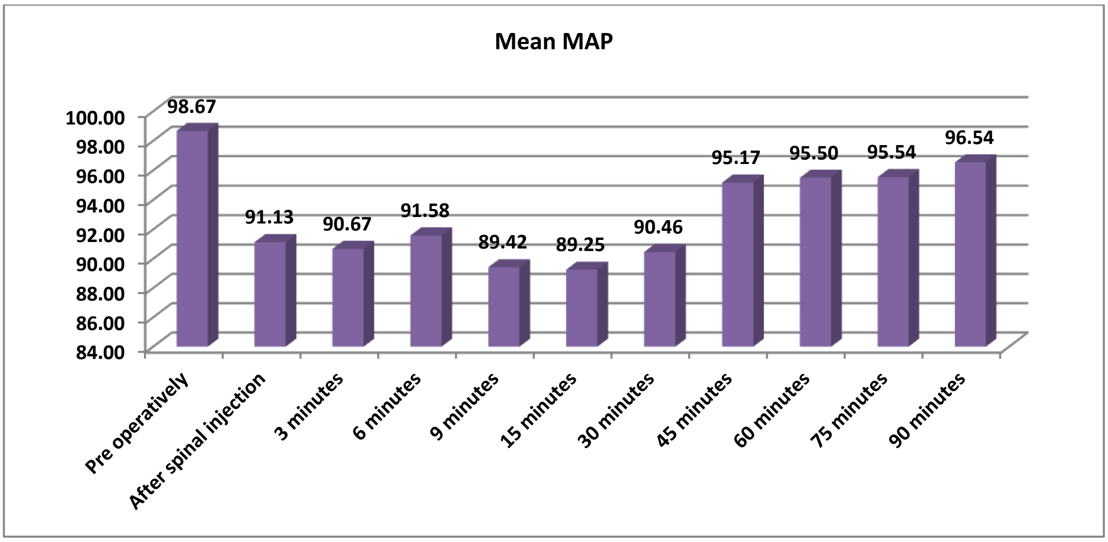

Fig-5: Mean MAP

Table-8: Block Characteristics

	Mean	Std. Deviation	Std. Error	Minimum	Maximum	Range
Duation of Surgey (in Min)	72.20	35.33	5.00	30	120	90
Onset time to T 10(Min) - Sensory Block	18.06	3.89	0.55	11	29	18
Time to achieve maximum height of block (min) - Sensory Block[PSBL]	20.50	4.73	0.67	14	28	14
Time to onset of regression at the level of L1 (min) - Sensory Block	76.68	6.55	0.93	64	89	25
Time to modified Bromage score 3(min) - Motor Block	2.66	0.48	0.07	2	3	1
Time to complete recovery(min) - Motor Block	172.20	9.78	1.38	152	190	38

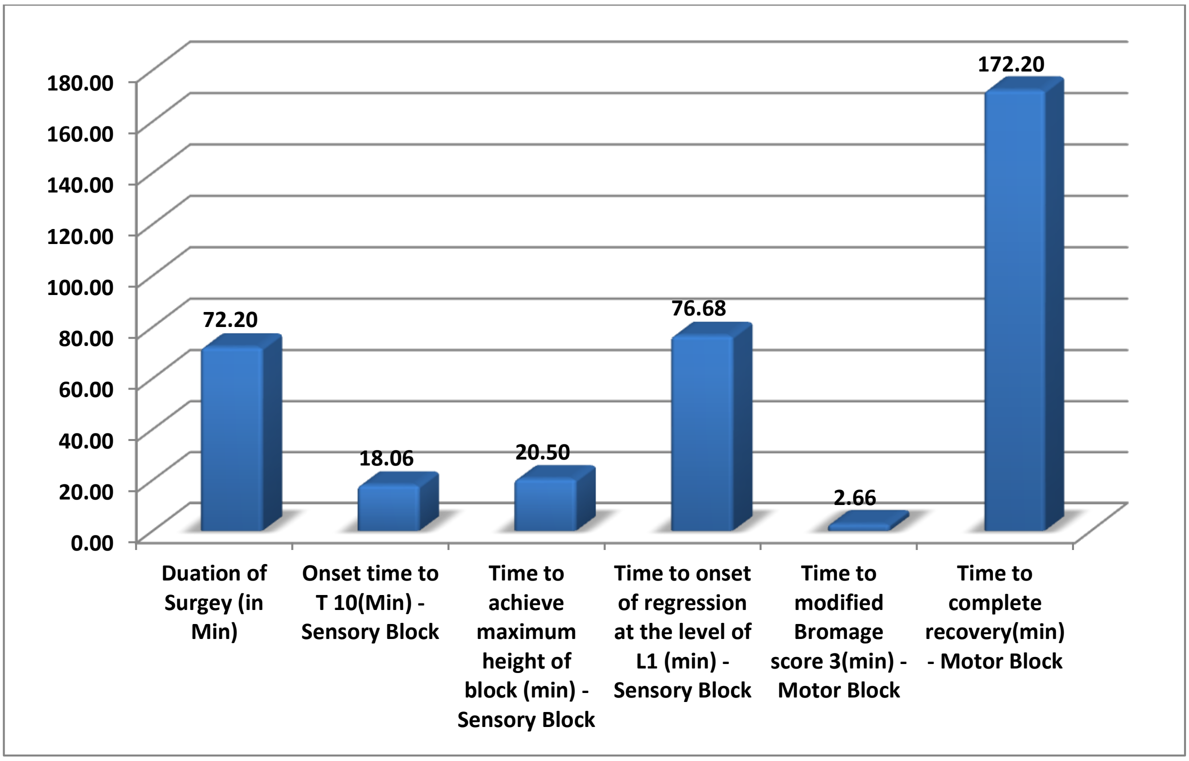

Fig-6: Block Characterstics

SIDE EFFECTS OBSERVED

Incidence of nausea, vomiting, hypotension, pain, shivering was 16%, 16%, 4%, 4%, 16% respectively.[Table 7]

Table-7: Side Effects

Side Effects	Number (Percentage)
Nausea	8 (16%)
Vomiting	8 (16%)
Hypotension	2 (4%)
Pain	2 (4%)
Shivering	8 (16%)

DISCUSSION

Levobupivacaine is a preferred local anaesthetic due to its longer sensory block, lower cardiac and central nervous system toxicity and shorter motor block. It produces localized anaesthesia by blocking the transmission of action potential in sensory, motor and sympathetic nerve fibers, by inhibiting the passage of sodium through voltage sensitive ion channels in the neuronal membrane [7].

There is a dose-dependent action of levobupivacaine with the duration of analgesia and at least 10 mg is required for spinal anaesthesia for sensory and motor block effectiveness [8]. There is a synergistic action of the Intrathecally administered fentanyl as an adjuvant to low dose local anaesthetics, by a direct action on the opioid receptors in the spinal cord [9]. Fentanyl stimulates both µ1 and µ2 receptors and potentiates the afferent sensory blockade [10]. As reported in the previous studies, the addition of 25 µg fentanyl to local anaesthetic improves anaesthesia quality and prolongs postoperative analgesia without prolonging the time to void [11].

The mean time taken for the Sensory block onset in the present study was 18.06±3.89. Similar to the results obtained in the present study, the studies by Taspinar *et al*. [12], Chatrath *et al*. [13] (4.57±0.50 minutes for combined spinal-epidural analgesia in labor) and Sahin *et al*. [14] found that sensory block onset time was significantly shorter in the levobupivacaine group.

The time to achieve maximum height of sensory block in the present study was 20.50±4.73 minutes which was significantly more in comparison to the study by Akcaboy *et al.* (11.27±1.42) minutes [15], Brahmbhatt *et al*. [16] (4.90±1.80), Del-Rio-Vellosillo *et al*. for lumbar disc surgeries [17], Sahin *et al*. (7±1.63 minutes) for lumbar disc surgeries [14] and 7.52 minutes with the levobupivacaine plus fentanyl combination in the study by Ozyilkan *et al*. [18] for the caesarean section. The shorter times in our study might be associated with the higher levobupivacaine doses.

The mean time to onset of regression for Sensory block at the level of L1 (min) was found to be 76.68±6.55 in the present study. This was found to be similar to the study by Guler *et al.* (71.43) [19], Turkmen *et al.* (63.40) [20], Akcaboy *et al*. [15] (67.41 minutes) and Goyal *et al.* (79.34) [21]. In the study by Chatrath *et al*. [13] the mean duration of spinal analgesia was 95.67±7.96, Chan and Chiu [22] using 2.5 mg levobupivacaine and 25 µg fentanyl intrathecally, the duration of analgesia was 101.4 ± 26.64 minutes, Hepner *et al*. [23] showed that the duration of intrathecal component of CSE group to be 91.1±32.6 minutes and Pascual-Ramirez *et al*. [24] found that the average duration of intrathecal analgesia was 113±93 minutes which was higher than the present study.

The time to onset of motor block in the present study was 2.66±0.48 minutes and duration of complete motor blockade was 172.20±9.78. Similarly, the development of motor block was faster and lasted longer with hyperbaric levobupivacaine which was found in the observations of Goyal *et al*. [21] Guler *et al*., [19] Subaşi *et al*. [25] and Turkmen *et al*. [26] In the study by Cuvas *et al*. [27] the duration of motor block was 213.75±59.49 minutes in Levobupivacaine with fentanyl group which was more than the present study.

In the study by Sahin *et al*. [14] the motor onset time for the levobupivacaine group was 7±3 minutes. The Time to modified Bromage score 3(min) -Motor Block was 2.66±0.48 minutes. In the study by Chen *et al*. [28] the time to motor block of Bromage 3 was 16.0±4.5 minutes.

In the study by Sahin *et al*. [14] Recovery times of sensory and motor blockade were found to be 175±57 and 216±59 minutes respectively for levobupivacaine group. This was dissimilar to the present study in which the recovery time for sensory block was 76.68±6.55 and motor block time was 172.20±9.78 which was much lesser.

Kuusniemi *et al*. [29] found that the addition of fentanyl 25 µg to 5 mg of bupivacaine for spinal anaesthesia resulted in effective anaesthesia with motor block of short duration. Akcaboy *et al*. [15] concluded that 5 mg 0.5% levobupivacaine with 25µg fentanyl usage in spinal anaesthesia can provide adequate sensorial blockade without motor block, stable haemodynamic profile and good patient and surgeon satisfaction for TURP surgery.

In studies where intrathecal levobupivacaine was used alone, motor block onset times were reported as 10.0 minutes by Glaser *et al*. [30] and as 15 minutes by Burke *et al*. [31]. In the present study, the addition of opioids to LA decreased onset times of motor block for levobupivacaine. One of the studies which compared the addition of fentanyl to intrathecal levobupivacaine on sensory and motor blocks, the time to maximum motor block was reported as being shorter in the 10 mg levobupivacaine plus fentanyl group [32]. As in the present study, motor and sensory block levels increased more rapidly in comparison to the control group; this effect was probably associated with the lipophilic character of sufentanil and fentanyl.

In the present study, decrease in SBP and DBP as well as changes in heart rate were in acceptable ranges. Similar findings were also found in the study by Goyal *et al*. [21] and Misirlioglu *et al*. [33] Erdil *et al.* [34] noted in spinal anaesthesia, better haemodynamic stability associated with low-dose levobupivacaine plus fentanyl compared with that seen with low-dose bupivacaine plus fentanyl.

Haemodynamic changes were also found to be similar to the present study in the study by D'Ambrosio *et al*. [35] for the patients undergoing modified stark method for caesarean delivery and Bremerich *et al*. [36] for caesarean section. In the study by Akcaboy *et al*. [34] the changes in the mean arterial pressure (MAP) and heart rate (HR) were found to be almost similar to the present study.

Bajwa and Kaur reported that [37] levobupivacaine produces the same adverse effects as seen with racemic bupivacaine and other local anaesthetics. The most common adverse drug reaction reported were hypotension (31%) followed by nausea (21%), vomiting (14%), headache (9%), procedural pain (8%) and dizziness (6%). However, the present study, the most common adverse effects reported were nausea (16%), vomiting (16%), shivering (16%) followed by pain (4%) and hypotension (4%).

CONCLUSION

It is concluded from our study that Levobupivacaine when combined with Fentanyl provided adequate subarachnoid block for lower abdominal surgeries. There was adequate surgical anaesthesia and hemodynamic stability achieved in terms of-

- Prolonged duration of sensory and motor block.
- Longer duration of post operative analgesia.
- Lesser number of doses of rescue analgesia required.

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