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# A RANDOMIZED, DOUBLE-BLINDED,CONTROLLED STUDY FOR COMPARATIVE EVALUATION OF INTRATHECAL ADMINISTRATION OF LEVOBUPIVACAINE WITH FENTANYL AND LEVOBUPIVACAINE WITH MAGNESIUM SULFATE(MGSO4) IN LOWER ABDOMINAL SURGERY FOR POST-OPERATIVE ANALGESIA

Anaesthesiology

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## ABSTRACT

**Context:** Intrathecal administration of levobupivacaine with fentanyl and levobupivacaine with magnesium sulfate for postoperative analgesia.

**Aim:** To compare the quality and duration of postoperative analgesia by addition of fentanyl or magnesium sulfate to levobupivacaine given intrathecally.

**Setting and Design:** The study was conducted as a Randomized, Double-Blinded, Controlled Study in a 1200 bedded teaching hospital.

**Materials and Methods:**60 patients undergoing lower abdominal surgery were randomly divided into two groups 30 each, group LF received 12.5 mg of 0.5% isobaric levobupivacaine with 25mcg fentanyl. Group LM received 12.5 mg of 0.5% isobaric levobupivacaine with 25mg of magnesium sulfate. Onset of sensory and motor block, duration and quality of analgesia was noted along with intraoperative hemodynamic parameters.

**Statistical Analysis:** Microsoft Excel 2010 with student 't' test (unpaired) and one way ANOVA were used for comparing the two groups.

**Results:** The addition of fentanyl to levobupivacaine prolonged the duration of sensory block(LF 235.83±18.10 vs LM 205.17±19.14),motor block(LF 190.5±13.60 vs LM 152.47±10.63) and duration of analgesia(LF 287.5±16.12 vs LM 246.33±19.38) compared to MgSO4 with $p<0.05$ found statistically significant.

**Conclusion:** Intrathecal levobupivacaine plus fentanyl prolonged the duration of sensory and motor block and provided prolonged duration of analgesia.

## KEYWORDS

Fentanyl, Magnesium Sulfate, Levobupivacaine

## INTRODUCTION

Management of acute pain following surgery has been one of the major concerns in anaesthetic practice. The need for prolonged post operative analgesia has led to the use of different adjuvants with the aim of prolonging the duration of block, better patient satisfaction, decreased resource utilization and faster recovery. Adequate pain management is essential to facilitate rehabilitation and functional recovery enabling patients to return to their normal activity at the earliest.

Levobupivacaine is a pure S (–) enantiomer of racemic bupivacaine which is used in similar doses as bupivacaine having a similar onset and duration; levobupivacaine potency appears to be slightly less than bupivacaine[1]. The majority of clinical studies using identical doses of levobupivacaine and bupivacaine have found no significant difference in clinical efficacy for spinal anaesthesia[2-4]. The main advantage of levobupivacaine is that it is less cardiotoxic than bupivacaine[5,6]

The addition of opioids to intrathecally administered local anaesthetic solution increases the duration of post operative pain relief. The effects of opioids within the CSF are complex because of a combination of direct spinal cord dorsal horn opioid receptor activation, cerebral opioid receptor activation after CSF transport, peripheral and central systemic effects after vascular uptake. The effect at each of these sites depends on both the dose administered and the physicochemical properties of the opioid particularly lipid solubility. Highly lipid-soluble drugs such as fentanyl and sufentanil have a more rapid onset and shorter duration of action than more hydrophilic opioids.

The anti-nociceptive effect of magnesium appears relevant not only in chronic pain[7] but also in the duration and intensity of post operative pain[8]. These effects are primarily based on regulation of calcium influx into the cell. Magnesium is a noncompetitive antagonist to NMDA receptors and thus prevents central sensitization from peripheral nociceptive stimulation.

The present study was designed to assess the effect of addition of fentanyl to levobupivacaine and MgSO4 to levobupivacaine in lower abdominal surgery for post-operative analgesia. The primary outcome variable was the time of first rescue analgesia requirement post-operatively and secondary outcome variables were intraoperative hemodynamics and complications if any.

## MATERIALS AND METHODS

This study is a prospective, randomized, double-blinded comparative study carried out at Swaroop Rani Nehru Hospital (associated to Motilal Nehru Medical College Prayagraj) over a period of one year. After approval from institutional ethical committee and obtaining written informed consent, 60 patients scheduled for lower abdominal surgery under spinal anaesthesia were included in this study.

### INCLUSION CRITERIA

Patients aged between18-60yrs of both sexes belonging to ASA physical status I and II undergoing elective lower abdominal surgery under spinal anaesthesia.

### EXCLUSION CRITERIA

1- Patients refusal.
2- ASA Class III & IV.
3- Patients less than 18 yrs and more than 60 yrs of age.
4-. Patients having cardiovascular disease and hypertension.
5- Patients having prior history of allergy to any of the drugs used in this study.
6- Patients having any neurologic and psychiatric illness.

Patients were randomly assigned to one of the two groups using a "slips of paper in a box" technique distributing 30 patients in each group. Double-blinding was ensured as both patient as well as performer of spinal anaesthesia were unaware of drug solution used.

**Group LF:** Patients in whom intrathecal 0.5% isobaric Levobupivacaine (12.5mg) with Fentanyl (25mcg) was administered.

**Group LM:** Patients in whom intrathecal 0.5% isobaric Levobupivacaine(12.5mg) with MgSO4(25mg) was administered .

Pre-anaesthetic check up was done a day prior to surgery and plan of

anaesthesia was explained to the patients. All patients received Tab.Alprazolam 0.25 mg orally on the night prior to surgery and were kept nil per oral past midnight. On arrival in operation theatre, venous cannulation was done and intravenous line was secured in one of the upper limbs. Electrocardiogram(ECG), Pulse oximetry(SpO2) and non invasive blood pressure(NIBP) were connected and preoperative vitals were recorded. After preloading the patients with Ringer Lactate 15ml/kg, lumbar puncture was performed with 25 gauge Quincke type spinal needle and the drug solution was injected intrathecally.

Level of sensory block was assessed by loss of sensation to pinprick using 22 gauge blunt tip needle in midclavicular line bilaterally.

Motor blockade was assessed by using the modified Bromage scale.

For assessment of post-operative analgesia, numerical rating scale (NRS- consisting of score 0 to 10 with score 0-no pain to score 10-worst possible pain) was explained to every patient preoperatively.

Inj. Diclofenac 1.5mg/kg body weight intramuscular was given as rescue analgesic if NRS >4 in post-operative period.

**Following Variables Were Assessed In Perioperative Period:**

1. Demographic data: Age in years, sex, weight in kilograms.
2. Duration of surgery.
3. Time for first requirement of analgesic supplement (time from completion of administration of spinal solution to first requirement of analgesic supplement when NRS>4)
4. Onset of sensory block: It is determined by the time from completion of administration of spinal anaesthetic solution to loss of pinprick sensation to T8 dermatome (checked every 30 seconds from spinal block till 15 minutes).
5. Onset of motor block: It is determined by the time from completion of administration of spinal anaesthetic solution to motor block upto modified Bromage score 3 (checked every 30 seconds from spinal block till 15 minutes).
6. Duration of sensory block: It is defined by time taken by sensory block to regress upto S1 dermatome (checked by pinprick method every 15 minutes following surgery).
7. Duration of motor block: It is defined by the time taken by motor block to recover upto modified Bromage score 0 (checked every 15 minutes following surgery).
8. Heart rate, Non invasive blood pressure (mean arterial pressure) and oxygen saturation(SpO2) were measured at 5, 15, 30, 45, 60, 75 and 90 minutes.
9. The duration of analgesia was recorded.
10. Duration of analgesia -time from completion of administration of intrathecal drug to first requirement of analgesic supplement(NRS ≥4).The NRS score of ≥4 constituted the end point of the study.
11. Complications if any, during intra operative or post operative phase were noted and properly taken care of.

Heart rate<60 was considered bradycardia and treated with Inj. Atropine 0.6mg IV.

A decrease in Mean arterial pressure>20% of the baseline was considered hypotension and treated with incremental dose of Inj.Mephentermine 6mg IV.

For nausea and vomiting Inj.Ondansetron 4mg IV was given.

## STATISTICALANALYSIS

All the data obtained were analysed statistically using Microsoft Excel 2010 and statistical software plug-ins. Student 't' test (unpaired and one way ANOVA) were used where appropriate to test the significance of data. Data are being presented as mean±SD and 'p' value<0.05 was considered significant and 'p' value< 0.001 was considered highly significant.

## RESULTS

The present study compared the clinical efficiency of fentanyl and magnesium sulfate as adjuvant to intrathecal 0.5% isobaric levobupivacaine in 60 consented patients scheduled for elective lower abdominal surgery under subarachnoid block.There was no protocol deviation and no patient was excluded from study after randomization. Surgical procedures were performed uneventfully and there were no surgical or anesthetic complications.

Patients of the two groups were statistically comparable regarding mean age, weight, height, gender, ASA physical status and surgical characteristics.

These two groups were statistically not significant regarding HR, MAP, and SpO2, P value>0.05

**Table 1:Onset Time Of Sensory Blocks In Two Groups**

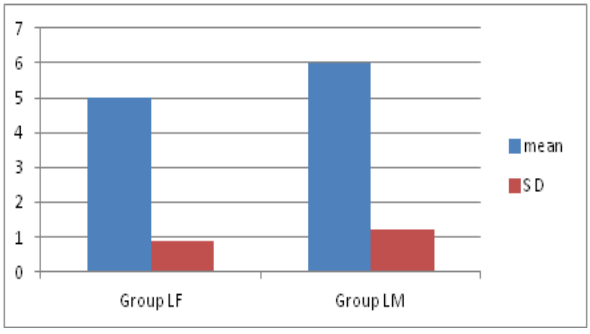
| Group | LF | LM | 'P' value |
|---|---|---|---|
| Mean± S D | 4.98±0.86 | 6±1.210 | 0.0004(S) |

**Comparison Between Two Groups**

| Group LF VS | 't' value | 3.763 |
|---|---|---|
| Group LM | 'p' value | 0.0004(S) |

S-SIGNIFICANT

Bar diagram of Onset time of Sensory Blocks in two groups(Table 1)



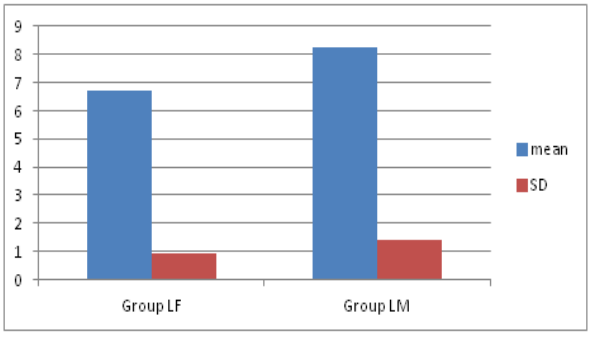

* Inference: Statistically significant(P<0.05).

**Table 2:Onset Of Motor Blocks In Two Groups**

| Group | LF | LM | 'P' value |
|---|---|---|---|
| Mean ±SD | 6.73±0.944 | 8.23±1.406 | 0.0001(S) |

**Comparison of motor block in two groups**

| Group LF Vs | 't'value | 4.851 |
|---|---|---|
| Group LM | 'P'value | 0.0001(S) |




Inference:statistically significant(p<0.05).

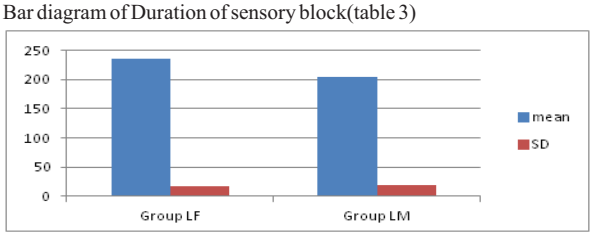
**Table 3:Duration Of Sensory Block In Two Groups**

| Group | LF | LM | 'P'value |
|---|---|---|---|
| mean± SD | 235.83±18.10 | 205.17±19.14 | 0.0001(S) |
| mean ± SD | 190.5±13.60 | 152.47±10.63 | 0.0001(S) |

**Comparison Between Two Groups**

| Group LF VS | 't'value | 6.374 |
|---|---|---|
| Group LM | 'P'value | 0.0001(S) |

Bar diagram of Duration of sensory block(table 3)




Inference: statistically significant(p<0.05).

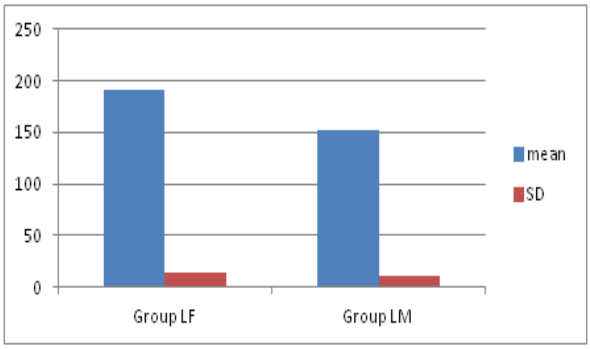
**Table 4:Duration of Motor blocks in two groups**

| Group | LF | LM | 'P'value |
|---|---|---|---|
| Mean ± SD | 190.5±13.60 | 152.47±10.63 | 0.0001(S) |

**Comparison between two groups**

| Group LF Vs | 't'value | 12.067 |
|---|---|---|
| Group LM | 'p'value | 0.0001(S) |

Bar diagram of duration of Motor block(table 4)




Inference: statistically significant($p<0.05$).

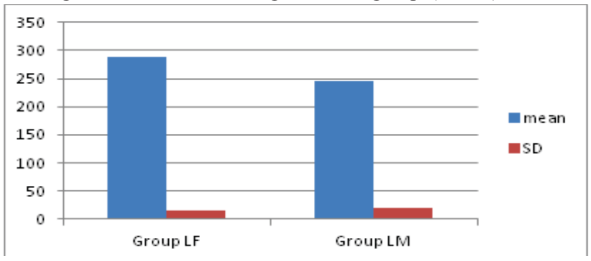
**Table 5: Duration of Analgesia in two groups**

| Group | LF | LM | 'p'value |
|---|---|---|---|
| Mean ±SD | 287.5±16.12 | 246.33±19.38 | 0.0001(S) |

**Comparison Between Groups**

| Group LF Vs | 't'value | 9.85 |
|---|---|---|
| Group LM | 'p'value | 0.0001(S) |

Bar diagram of Duration of Analgesia in two groups(table 5)




Inference: statistically significant($p<0.05$).

## DISCUSSION

Primary aim of the present study was to compare the post-operative analgesic requirement on addition of fentanyl or magnesium sulfate to low-dose intrathecal levobupivacaine in lower abdominal surgeries under subarachnoid block.

The combination of additives to local anaesthetics is found to be synergistic producing analgesia for prolonged duration without increasing the duration of sympathetic or motor blockade thus allowing early ambulation of patients and reduction in dosages of local anaesthetics hence a decline of their systemic side effects.

The study demonstrated that the groups of patients receiving fentanyl or magnesium sulfate with low-dose levobupivacaine for lower abdominal surgeries were comparable with respect to age, weight, height and sex.

There was no statistically significant difference in heart rate, blood pressure(MAP), oxygen saturation and duration of surgery between the two groups of patients.

In the present study the onset of sensory and motor blockade was shorter who received fentanyl with levobupivacaine than those who received magnesium sulfate with levobupivacaine.

The early onset with fentanyl can be attributed to its lipophilic properties. The lipophilic opioids rapidly traverse the dura mater, rapidly penetrate the spinal cord where they bind the opioid receptors within the white matter as well as dorsal horn receptors and eventually enter the systemic circulation. The delayed effect on the onset sensory and motor block with magnesium sulfate suggests that it acts only at the spinal cord.

The study also demonstrated the prolonged sensory and motor block duration by addition of fentanyl with intrathecal levobupivacaine.

**Manjunath Bidikar** et al[9] studied the effects of intrathecal levobupivacaine and intrathecal levobupivacaine with fentanyl in 60 patients undergoing cesarean section. Group L: levobupivacaine. Group F: levobupivacaine plus fentanyl. Prolonged duration of postoperative sensory block and rescue analgesia was found in Group F as compared to Group L and duration of motor blockade was prolonged in Group L and $P< 0.05$ was found statistically significant. Intrathecal levobupivacaine plus fentanyl prolonged duration of sensory block and rescue analgesia.

In our study intrathecal fentanyl with levobupivacaine was associated with earlier onset of sensory (4.98±0.86 min) and motor block(6.73±0.944 min) and prolonged duration of sensory(235.83±18.10) and motor block(190.5±13.60) with prolonged duration of analgesia(287.5±16.12). All these results were statistically significant($p <0.05$).

**Girgin NK, et al**[10] investigated the addition of 25 mcg intrathecal fentanyl to levobupivacaine spinal anaesthesia for outpatient inguinal herniorrhaphy allows a sub-anaesthetic levobupivacaine dose to be used. The results indicate that for outpatient inguinal herniorrhaphy, intrathecal fentanyl combined with low-dose levobupivacaine provides good quality spinal anaesthesia and minimizes the need for intra-operative analgesic agent.

The results of our study are consistent with that of this study as we also found that intrathecal fentanyl with levobupivacaine provides good analgesia during surgery and there was no requirement of sedative agents intra operatively.

**Krobot, R; et al**[11] compared the effect of intrathecal levobupivacaine with or without fentanyl in patients undergoing transurethral urologic surgery. Levobupivacaine plus fentanyl provide adequate spinal anaesthesia, better postoperative analgesia and less cardivascular effects than levobupivacaine in patients undergoing transurethral urologic surgery.

The result of our study is consistent with this study as fentanyl with levobupivacaine provide prolonged duration of analgesia(287.5±16.12) and hemodynamic stability.

**Akan et al**[12] did a study by using plain levobupivacaine and comparing it with levobupivacaine plus fentanyl and levobupivacaine plus sufentanil in patients undergoing transurethral resection of the prostate under spinal anaesthesia concluded that combining lower doses of levobupivacaine with fentanyl and sufentanil provides faster onset of sensory block, lower frequency and shorter duration of motor block and prolonged analgesia time.

Our study also shows earlier onset of sensory(4.98±0.86) and motor block(6.73±0.944) with prolonged duration of post-operative analgesia(287.5±16.12 vs 246.33±19.38) while using levobupivacaine with fentanyl.

**Wasudeo Sadashio Barsagde, et al**[13] compared the effects of intrathecal levobupivacaine-fentanyl and levobupivacaine on quality of subarachnoid block and haemodynamic variations in caesarean deliveries. Addition of fentanyl to intrathecal levobupivacaine, prolonged duration of sensory and motor block with faster onset of sensory and motor block with better quality as compared to levobupivacaine. Intrathecal levobupivacaine with fentanyl was found to improve the quality and prolonged duration of intrathecal block. It reduced the need for rescue analgesia/supplementary analgesics for postoperative pain relief without any significant side effects.

Similar to the above study, we also found that intrathecal fentanyl with levobupivacaine caused prolonged duration of post-operative analgesia(287.5±16.12 vs246.33±19.38).

## CONCLUSION

The aim of combination of additives to intrathecal local anaesthetics is to produce prolonged post-operative analgesia without increasing

sympathetic or motor blockade thus reducing the dosage of local anaesthetics and their side effects. Fentanyl 25mcg when used as adjuvant to 12.5 mg of 0.5% isobaric levobupivacaine for intrathecal block during lower abdominal surgeries delayed the requirement of rescue analgesia, produced faster onset and prolonged duration of sensory and motor block.

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