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ORIGINAL RESEARCH

Premixed vs sequential intrathecal administration of levobupivacaine with magnesium as an adjuvant in surgeries below umbilicus

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ABSTRACT

Introduction-The alleviation of pain during surgery is crucial for ensuring a smooth surgical experience for patients. Several investigations have indicated that premixing adjuvants with local anaesthetics can modify the distribution of the medication in the cerebrospinal fluid (CSF). Consequently, providing adjuvants in separate syringes may mitigate the alteration in density of both medications, thereby preventing changes in cerebrospinal fluid distribution. The aim of present study is to assess the premixed vs sequential intrathecal administration of levobupivacaine with magnesium as an adjuvant in surgeries below umbilicus**Material and methods-**This prospective randomized controlled trial was conducted in the department of anesthesiology and critical care, GMCH Kathua in patients scheduled for elective lower abdominal or lower limb surgeries below the umbilicus under spinal anesthesia for a period of one year. Participants were randomized into three groups with 50 patients in each group. In group A,3ml of 0.5% levobupivacaine and 100mg(0.5ml) magnesium sulphate was combined in a single 5ml syringe before intrathecal injection. In the group B, magnesium sulphate100mg(0.5ml) was administered first in 2ml syringe followed by levobupivacaine 0.5% (3ml) was given in a separate 5ml syringe. In group C, levobupivacaine 0.5% (3ml) was administered in a separate 5ml syringefirst, followed by magnesium sulphatesulphate100mg(0.5ml) was administered in a separate 2ml syringe.Demographic data, medical history, intraoperative variables, and postoperative outcomes were recorded. **Results–**Group B's heart rates were consistently considerably lower than those of Groups A and C ($p < 0.05$). Between 5 and 30 minutes after the intervention, Group B's heart rates were consistently considerably lower than those of Groups A and C ($p < 0.05$).Group B showed the fastest onset of sensory (3.5 ± 0.7 min) and motor block (4.9 ± 0.6 min) ($p < 0.05$). Furthermore, Group B took the smallest amount of time (6.4 ± 0.6 min) to reach maximal sensory block, followed by Group C. Group A took the longest (9.1 ± 1.0 min). In comparison to Groups A and C, Group B also required the fewest rescue analgesic doses in the first 24 hours (2.5 ± 0.2) and had a considerably longer duration of analgesia, as seen by the longest time to first rescue analgesia (350.1 ± 18.3 min). Better pain management was indicated by Group B's lowest VAS values at all recorded intervals after the first hour.**Conclusion–**Our study found that sequential magnesium administration before levobupivacaine injection accelerates action, prolongs sensory and motor blockade, prolongs postoperative analgesia, and reduces rescue analgesia, compared to premixed magnesium with levobupivacaine.

Keywords- Adjuvant, Levobupivacaine, Magnesium Sulphate, Premixed, Sequential

INTRODUCTION

Management of acute pain following surgery has been one of the major concerns in anesthetic practice. Spinal anesthetic has emerged as a fundamental technique in lower abdomen and lower limb procedures owing to its effectiveness, fast onset, and reliable block properties. Levobupivacaine, a prolonged-action local anesthetic, has become favoured due to its decreased cardiotoxicity relative to racemic bupivacaine.[1]

Magnesium sulfate demonstrates analgesic and anesthetic-sparing effects due to its NMDA receptor antagonism and calcium channel blocking characteristics. The concurrent injection of

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magnesium sulfate with levobupivacaine intrathecally has been examined as a potential method to extend the duration and enhance the quality of spinal anesthesia for procedures below the umbilicus.[2]

Certain investigations have noted that premixing adjuvants with a local anaesthetic solution may modify the distribution of the medication in the cerebrospinal fluid (CSF). Therefore, giving adjuvants in separate syringes may mitigate the alteration in density of both medications, thereby preventing changes in cerebrospinal fluid distribution.[3]

This study seeks to compare two administration ways of levobupivacaine with magnesium sulfate as an adjunct: premixed and sequential. In the premixed approach, levobupivacaine and magnesium sulfate are amalgamated prior to intrathecal injection, whereas in the sequential technique, they are supplied in succession. Both strategies have been suggested to maximize the interaction between the local anesthetic and the adjuvant, potentially improving the block properties and perioperative results.

The comparison of premixed and sequential administration methods entails assessing multiple parameters, including onset time, duration of sensory and motor blockade, hemodynamic stability, intraoperative analgesic needs, postoperative pain scores, adverse effects, and overall patient satisfaction. Comprehending the distinctions among these procedures can yield significant insights into enhancing spinal anesthetic protocols for surgeries beneath the umbilicus, potentially augmenting patient outcomes and perioperative management measures.

MATERIAL AND METHODS

This prospective randomized controlled trial was conducted in the department of anesthesiology and critical care, GMCH Kathua in patients scheduled for elective lower abdominal or lower limb surgeries below the umbilicus under spinal anesthesia for a period of one year. Ethical clearance was taken from institutional ethics committee of college and written informed consent was taken from patients after explaining them the procedure of the study.

Calculation of sample size was done on the basis of findings from a previous study to ensure adequate power to detect differences between the groups.A difference between the groups of more than 20-25% was considered as a practical significant. Using α = 5% and β = 90%, the sample size can be estimated by using the formula given by:-

$n= \frac{Z^2 * p(1-p)}{l^2}$

Where:

z=1.96

P=0.5, (50%)

Q=1-P= 1-0.5 = 0.5

l (Precision) = 15%; (5% to 20%)

95% confidence interval.

5% level of Significance

N=150 (Approximate)

Sample Size (n)= 50 Patients in each Group.

Patients were selected on the basis of inclusion and exclusion criteria:

Inclusion criteria

- Adults aged 18-65 years
- American Society of Anesthesiologists (ASA) physical status I or II
- willing to participate in the study and provide a willing written informed consent.

Exclusion criteria

- Contraindications to spinal anesthesia
- Pregnancy
- Chronic medical illness like renal, cardiac and pulmonary diseases
- ASA 3 and 4 patients
- History of allergy to study medications
- Inability to provide informed consent.

Methodology

Participants were randomized into three groups with 50 patients in each group. In group A, 3ml of 0.5% levobupivacaine and 100mg(0.5ml) magnesium sulphate was combined in a single 5ml syringe before intrathecal injection. In the group B, magnesium sulphate 100mg(0.5ml) was administered first in 2ml syringe followed by levobupivacaine 0.5% (3ml) was given in a separate 5ml syringe. In group C, levobupivacaine 0.5% (3ml) was administered in a separate 5ml syringe first, followed by magnesium sulphate sulphate 100mg(0.5ml) was administered in a separate 2ml syringe.Demographic data, medical history, intraoperative variables, and postoperative outcomes were recorded.

The primary outcome measures included onset of sensory and motor block, duration of sensory and motor block, and intraoperative hemodynamic stability. Secondary outcome measures included postoperative analgesic requirements, postoperative pain scores and overall patient satisfaction.Demographic data, medical history, intraoperative variables, and postoperative outcomes were recorded.

The Bromage scale was employed to assess the motor blockade. Score 0: The patient is capable of moving their hip, knee, and ankle. Score 1: The patient is capable of moving their knee and ankle, but not their hip. Score 2: The patient is capable of ankle movement but lacks mobility in the hip and knee. Score 3: The patient is unable to mobilise their hip, knee, or ankle.

The surgical procedure commenced upon achieving the requisite level of anaesthesia.

The interval from the conclusion of the anaesthetic injection to the onset of insensitivity to a pinprick at the T10 level was utilised to ascertain the initiation of sensory blockade. The interval from the conclusion of the study drug injection to the achievement of Bromage I was utilised to ascertain the commencement of motor blockade.

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The interval between the conclusion of the research drug injection and the moment the block achieved the T6 dermatome was utilised to define the maximum sensory blockade accomplishment.

The interval between the conclusion of the study drug injection and the documentation of Bromage grade 3 was utilised to delineate the peak motor blockade attained.

VAS score was defined as scale for recording pain where Score: 0-2 Absence of discomfort, Scores of 2-4 signify mild pain, 4-6 denote moderate pain, 6-8 represent severe pain, while 8-10 imply terrible pain.

The duration of the initial rescue analgesia was defined as the interval from the intrathecal injection until the VAS exceeded 4, and the quantity of rescue analgesia administered over 24 hours was recorded when the VAS score over 4 in both groups.

Statistical analysis

Descriptive statistics was used to summarize demographic and clinical characteristics. Continuous variables were analyzed using t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were analyzed using chi-square tests. A p-value <0.05 will be considered statistically significant. SPSS version 25.0 was used for statistical analysis.

RESULTS

Table 1 shows the demographic and baseline clinical characteristics of patients in Groups A, B, and C. The mean age, height, weight, and duration of surgery were comparable across all three groups, with no statistically significant differences observed ($p > 0.05$). The distribution of ASA physical status grades was also similar among the groups, with the majority of patients classified as ASA Grade I.

Table 1: Demographic Data of patients among three groups

Parameter	Group A	Group B	Group C	p-value
Age (Mean ± SD, years)	45.3 ± 7.8	46.1 ± 7.5	45.9 ± 8.0	0.827
ASA Grade I (%)	28 (56%)	30 (60%)	27 (54%)	-
ASA Grade II (%)	22 (44%)	20 (40%)	23 (46%)	-
Height (cm)	158.2 ± 5.3	158.5 ± 4.9	157.9 ± 5.6	0.903
Weight (kg)	61.4 ± 6.8	62.1 ± 7.1	61.9 ± 6.9	0.879
Duration of surgery (min)	128.4 ± 11.2	127.9 ± 10.8	129.1 ± 10.7	0.912

The mean heart rate readings (in beats per minute) for Groups A, B, and C for a 24-hour period are shown in Table 2 at predetermined intervals. All groups' baseline heart rates were similar ($p = 0.813$). But between 5 and 30 minutes after the intervention, Group B's heart rates were consistently considerably lower than those of Groups A and C ($p < 0.05$). The groups' heart rate measurements started to converge after 60 minutes, and no statistically significant differences were seen after that time ($p > 0.05$).

Table 2 Comparison of Mean Heart Rate (beats/min) among three groups

Time Interval	Group A	Group B	Group C	p-value
Baseline	82.4 ± 4.5	81.9 ± 4.7	82.1 ± 4.3	0.813
5 min	79.2 ± 3.9	75.4 ± 3.5	77.1 ± 3.8	<0.05*
10 min	79.3 ± 4.2	76.2 ± 3.6	78.3 ± 3.9	<0.05*
15 min	80.0 ± 4.1	77.7 ± 3.7	78.8 ± 3.8	<0.05*
30 min	81.2 ± 3.8	78.1 ± 3.6	79.5 ± 3.9	<0.05*
60 min	81.1 ± 4.0	80.2 ± 4.1	80.3 ± 4.2	0.091
120 min	82.0 ± 4.1	81.3 ± 4.0	81.5 ± 4.3	0.388
240 min	82.5 ± 3.9	82.0 ± 3.8	82.2 ± 3.9	0.713
360 min	82.8 ± 3.7	81.8 ± 3.6	81.9 ± 3.7	0.752
720 min	82.5 ± 3.8	81.5 ± 3.7	81.6 ± 3.6	0.698
1440 min	81.8 ± 4.1	81.2 ± 4.2	81.4 ± 4.0	0.672

The comparison of mean arterial pressure (MAP) readings throughout a 24-hour postoperative period for groups A, B, and C is shown in Table 3. Group B continuously showed the lowest results (92.1 ± 4.5 mmHg), Group C showed intermediate readings (94.3 ± 4.3 mmHg), and Group A showed the highest MAP (96.5 ± 4.2 mmHg) at baseline. Multiple time periods showed significant differences in MAP, particularly at 5, 10, 15 and 30minutes ($p < 0.05$), suggesting that the groups' haemodynamic response varied statistically significantly in the early postoperative phase. Group A maintained higher MAP levels throughout the monitoring period than Groups B and C, despite the fact that the disparities tended to becoming smaller over time.

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Table 3 Comparison of Mean arterial pressure (mm/Hg) among three groups

Time Interval	Group A	Group B	Group C	p-value
Baseline	96.5 ± 4.2	92.1 ± 4.5	94.3 ± 4.3	0.017*
5 min	95.8 ± 4.0	90.7 ± 4.3	93.2 ± 4.1	<0.01*
10 min	95.4 ± 3.8	91.0 ± 4.2	93.0 ± 4.0	<0.01*
15 min	94.9 ± 3.9	90.6 ± 4.1	92.5 ± 4.1	<0.01*
30 min	94.2 ± 3.7	89.9 ± 3.9	91.7 ± 3.8	<0.01*
60 min	93.6 ± 3.8	90.2 ± 4.0	91.5 ± 3.9	0.054
120 min	93.2 ± 3.9	90.8 ± 3.7	91.4 ± 4.0	0.067
240 min	93.5 ± 3.6	91.1 ± 3.8	91.8 ± 3.7	0.054
360 min	93.3 ± 3.5	91.0 ± 3.6	91.6 ± 3.5	0.061
720 min	93.7 ± 3.7	91.3 ± 3.7	91.9 ± 3.6	0.059
1440 min	94.0 ± 3.9	91.5 ± 3.8	92.1 ± 3.9	0.058

Table 4shows the three study groups' analgesic needs over a 24-hour period, together with the sensory and motor block's start and duration parameters. In comparison to Groups A and C, Group B showed the fastest onset of sensory (3.5 ± 0.7 min) and motor block (4.9 ± 0.6 min) ($p < 0.05$). Furthermore, Group B took the smallest amount of time (6.4 ± 0.6 min) to reach maximal sensory block, followed by Group C. Group A took the longest (9.1 ± 1.0 min). In comparison to Groups A and C, Group B also required the fewest rescue analgesic doses in the first 24 hours (2.5 ± 0.2) and had a considerably longer duration of analgesia, as seen by the longest time to first rescue analgesia (350.1 ± 18.3 min).

Table 4: Comparison of Block Characteristics and Analgesia among three groups

Parameter	Group A	Group B	Group C	p-value
Onset of sensory block (min)	5.8 ± 0.9	3.5 ± 0.7	4.1 ± 0.8	<0.05*
Onset of motor block (min)	6.9 ± 0.8	4.9 ± 0.6	5.3 ± 0.7	<0.05*
Time to maximal sensory block (min)	9.1 ± 1.0	6.4 ± 0.6	7.2 ± 0.7	<0.05*
Time to first rescue analgesia (min)	290.4 ± 17.2	350.1 ± 18.3	328.6 ± 17.9	<0.05*
No. of rescue analgesics in 24 hrs	3.0 ± 0.3	2.5 ± 0.2	2.7 ± 0.3	<0.05*

The mean Visual Analogue Scale (VAS) ratings for each of the three groups throughout a 24-hour period are summarised in Table 5. There was no statistically significant difference in pain scores at one hour after surgery, and they were modest and similar between groups ($p = 0.073$). In contrast, Group A continuously reported significantly higher VAS scores at 4, 6, and 12 hours ($p < 0.05$) than Groups B and C. Better pain management was indicated by Group B's lowest VAS values at all recorded intervals after the first hour. All groups experienced a decrease in pain levels after 24 hours, and the differences were no longer statistically significant ($p = 0.081$).

Table 5: Comparison of VAS Score Over 24 Hours among three groups

Time Interval	Group A	Group B	Group C	p-value
1 hr	0.8 ± 0.3	0.6 ± 0.2	0.7 ± 0.3	0.073
4 hr	2.9 ± 0.4	2.1 ± 0.3	2.4 ± 0.4	<0.05*
6 hr	4.1 ± 0.5	3.2 ± 0.4	3.5 ± 0.5	<0.05*
12 hr	3.7 ± 0.4	2.8 ± 0.3	3.1 ± 0.4	<0.05*
24 hr	2.2 ± 0.3	1.8 ± 0.2	2.0 ± 0.3	0.081

All the groups had nausea and vomiting at comparatively lower rates; Group B had a somewhat greater incidence (24%) than Group C (22%) and Group A (18%) as shown in Table 6.

Table 6: Adverse Effects

Adverse Effect	Group A, n(%)	Group B, n(%)	Group C, n(%)
Nausea/Vomiting	9 (18%)	12 (24%)	11 (22%)

DISCUSSION

The present prospective randomized controlled trial was conducted in the department of anesthesiology and critical care, GMCH Kathua in patients scheduled for elective lower abdominal or lower limb surgeries below the umbilicus under spinal anesthesia for a period of one year to compare premixed vs sequential intrathecal administration of levobupivacaine with magnesium as an adjuvant.

We divided the patients under three groups on the basis of different intervention given. In group A,3ml of 0.5% levobupivacaine and 100mg(0.5ml)

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magnesium sulphate was combined before intrathecal injection. In the group B , magnesium sulphate was administered first followed by levobupivacaine. In group C levobupivacaine was administered first, followed by magnesium sulphate. Past research indicates that the incorporation of adjuvants into analgesic may alter its distribution in the cerebrospinal fluid (CSF). Conversely, the sequential delivery of adjuvants in distinct syringes may restrict alterations in the density of both medicines, hence inhibiting any variation in cerebrospinal fluid distribution.[3] In a comparative study, Shivashankar A et al. found that the sequential administration of adjuvant with analgesic yields an earlier onset of action, an extended duration of sensory blockade, and a prolonged duration of postoperative analgesia, as opposed to the administration of premixed adjuvant with analgesic. [4]

In our study we found similar results indicating better efficiency of sequential administration of magnesium sulphate before implication of levobupivacaine. In Group B's heart rates and MAP were consistently considerably lower than those of Groups C and A ($p < 0.05$), indicating a stronger and earlier sympathetic blockade in group B, with stabilization of heart rate and mean arterial pressure in both C and A group as post operative period progressed. Group B had better postoperative pain management and block characteristics, most likely as a result of a more successful anaesthetic regimen.

In a study by Cesuretet al on the effects of sequential administration of hyperbaric and ordinary bupivacaine in patients resulted in reduced hypotension and diminished vasopressor requirements among patients who received the medicines in succession.[5]

Arora MV et al. compared the duration of analgesia, sensory block, and motor block in lower limb surgeries following intrathecal administration of clonidine-bupivacaine (Group C), buprenorphine-bupivacaine (Group B), and bupivacaine alone (Group A), and found that buprenorphine exhibits a prolonged effect. [6] A study conducted by Chaudhry G et al. examined the efficacy of premixed versus sequential administration of dexmedetomidine as an adjunct to intrathecal hyperbaric bupivacaine. They discovered that the duration required to attain the T10 spinal level was markedly reduced in the sequential group compared to the premixed group. Likewise, patients in the sequential group attained Modified Bromage III sooner than those in group P. [3]

A study by Soumya S et al. demonstrated a comparison between intrathecal buprenorphine and intrathecal dexmedetomidine for postoperative analgesia in lower abdomen and lower limb procedures. Group B was administered intrathecal 150 µg of Buprenorphine in conjunction with 15 mg of heavy 0.5% Bupivacaine, whereas Group D received intrathecal 15 µg of dexmedetomidine alongside 15 mg of heavy 0.5% Bupivacaine. It was observed that the duration until the first rescue analgesia in the postoperative period was significantly prolonged in Group B compared to Group D.[7]

In a study conducted by Hasaraddi GS et al found that the mean heart rate, mean arterial pressure (MAP), duration until the onset of sensory block, motor block, time to maximal blockade, and regression time to T10 were compared between the two groups, revealing a statistically significant difference. Both groups had statistically significant VAS values at 4, 6, and 12 hours; however, group S demonstrated superior postoperative pain alleviation compared to group M.[8]

Omar H et al in their randomized control trial found that Preoperative and intraoperative epidural Mg infusion with levobupivacaine resulted in prolonged postoperative analgesia and lower VAS. [9]

Mild gastrointestinal disturbances were distributed relatively evenly across the groups, with no marked predominance.Kogler et al discovered in their study that the preoperative administration of epidural magnesium followed by infusion yielded superior postoperative analgesia, reduced analgesic consumption, and a diminished occurrence of postoperative shivering, nausea, and vomiting. The primary distinctions included varying sites of action, specifically thoracic epidural, differing anaesthetic techniques such as general anaesthesia, the incorporation of two adjuvants to epidural levobupivacaine, namely sufentanil and MgSO4, and the sustained postoperative application of epidural analgesia. [10]

CONCLUSION

Our study revealed that the sequential administration of magnesium before injecting levobupivacaine leads to an expedited onset of action, an extended duration of sensory and motor blockade, a prolonged period of postoperative analgesia, and a reduced requirement for rescue analgesia compared to the administration of premixed magnesium with levobupivacaine.

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