

## EFFECT OF INTRATHECAL NALBUPHINE AND MAGNESIUM SULPHATE USED AS ADJUVANTS WITH BUPIVACAINE IN SPINAL ANAESTHESIA FOR LOWER ABDOMINAL SURGERY: A COMPARISON

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### ABSTRACT

#### BACKGROUND

Nalbuphine, a semi-synthetic, mixed agonist-antagonist opioid, has a potential to attenuate the mu-opioid effects and to enhance the kappa-opioid effects. The use of different adjuvants including Nalbuphine with local anaesthetics extends the duration of surgical anaesthesia including postoperative analgesia.

#### METHODS

Randomised, double blinded, case control study conducted in 100 adult ASA I and II patients divided randomly into two groups of 50 each undergoing lower abdominal surgeries Group M received (100 mg/0.2 mL) 50% preservative free Magnesium Sulfate and Group N received (0.8 mg/0.2 mL) 0.4% Nalbuphine along with 3 mL of 0.5% heavy bupivacaine each intrathecally.

#### RESULT

The onset of T10 sensory block  $5.75 \pm 0.74$  min. in group M and  $4.20 \pm 0.67$  min. in group N, which is significantly faster in group N ( $p < 0.0001$ ). Time of regression to S1 sensory level is  $199.44 \pm 10.41$  min. in group M and  $154.84 \pm 8.11$  min. in group N, which is prolonged in group M ( $p < 0.0001$ ). The mean time for rescue analgesia in group M is  $241.06 \pm 19.61$  minutes and group N is  $257.30 \pm 28.50$  min., which is statistically significant ( $P$  value=0.0013), i.e. prolonged postoperative analgesia in group N.

#### CONCLUSION

Nalbuphine has faster onset of anaesthesia and provides prolonged postoperative analgesia compared to magnesium sulphate when used as adjuvants with bupivacaine in spinal anaesthesia.

#### KEYWORDS

Intrathecal, Nalbuphine, Magnesium Sulphate, Postop Analgesia.

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#### INTRODUCTION

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."<sup>(1)</sup>

Regional anaesthesia is a safe, effective and inexpensive anaesthesia with an added advantage of long duration of postoperative analgesia. With epidural block, catheter have been used to produce prolonged postoperative analgesia while with spinal anaesthesia many adjuvants are used with local anaesthetic agent to increase the total duration of effective analgesia. Magnesium sulphate blocks NMDA channels in a voltage dependent fashion and such NMDA antagonism can prevent the induction of central sensitisation from peripheral nociceptive stimulation.<sup>(2)</sup>

Nalbuphine, a semi-synthetic, mixed agonist-antagonist opioid, has a potential to attenuate the mu-opioid effects and

to enhance the kappa-opioid effects. It was synthesised in an attempt to produce analgesia without the undesirable side effects of a  $\mu$  opioid receptor agonist. Previous studies have shown that epidural or intrathecal administration of Nalbuphine produces a significant analgesia accompanied by minimal pruritus and respiratory depression.<sup>(3,4,5)</sup> Culebras et al in 2002 used intrathecal Nalbuphine in doses 0.2, 0.8 and 1.6 mg with 10 mg of 0.5% hyperbaric Bupivacaine in patients undergoing caesarean section under Subarachnoid Block (SAB) and found 0.8 mg of Nalbuphine as an effective dose.<sup>(6)</sup> This study was undertaken to evaluate efficacy of intrathecally administered Bupivacaine with Magnesium sulphate and Bupivacaine with Nalbuphine for onset and duration of sensory and motor block, haemodynamic stability, duration of effective analgesia including postop analgesia and any adverse effects with each combination in patients undergoing lower abdominal surgeries.

#### BACKGROUND

The use of different adjuvants with local anaesthetics extends the duration of surgical anaesthesia including postoperative analgesia.

#### AIMS AND OBJECTIVES OF THE STUDY

This study was conducted to evaluate the effect of Magnesium sulfate and Nalbuphine when added to Bupivacaine for

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instituting central neuraxial block. In group M Magnesium Sulphate and in group N Nalbuphine was taken as adjuvant with Bupivacaine to produce Central neuraxial block. Both these groups were compared.

- To compare the onset of sensory and motor block.
- To compare the duration of sensory and motor block.
- To assess the duration of postop analgesia obtained in both the groups.
- To compare preop and postop haemodynamic changes and side effects.

## MATERIAL AND METHODS

The prospective, double blinded, randomised case control study was conducted within a period of 6 months from 1st December 2015 to 30th May 2016 in 100 adult ASA I and II patients divided randomly into two groups of 50 each undergoing lower abdominal surgeries after approval from Hospital Ethical Committee of Silchar Medical College and Hospital. After obtaining written and informed consent, Group M received (100 mg/0.2 mL) 50% preservative free Magnesium Sulphate and Group N received (0.8 mg/0.2 mL) 0.4% Nalbuphine along with 3 mL of 0.5% heavy Bupivacaine each intrathecally. Total volume of drug in both the groups was 3.2 mL. Sensory and motor block characteristics were studied. Duration of rescue analgesia noted and any side effect observed. Data analysed by GraphPad InStat software using appropriate statistical test. For qualitative data, chi-square test was used. Quantitative data were analysed using student's t-test.

### The P value was determined.

- $P > 0.05$  is not significant.
- $P < 0.05$  is significant.
- $P < 0.001$  is highly significant.

Following observations were made during the course of the study.

## STUDY PROTOCOL

### Preanaesthetic Assessment

- Detailed preoperative evaluation including history, investigations and physical examination done on the previous day of surgery.
- Procedure explained to the patient and patient was informed to communicate about the perception of any intraoperative discomfort or pain.
- Explained about VAS score.
- Written informed consent was taken from the patients and his/her relatives.

### Equipment

Equipment used in the study consist of:

- An autoclaved tray containing instruments used for antiseptic draping.
- Disposable 23G lumbar puncture needle.
- Disposable 5 cc syringe.
- Disposable tuberculin syringe.

### Drugs

- Inj. Bupivacaine 0.5% heavy ampoule.
- Inj. Magnesium sulphate 50% preservative free ampoule.

- Inj. Nalbuphine 1%, which was made as 0.4% by diluting its 1 mL to 2.5 mL with distilled water.

### In the Operation Theatre

- IV line secured and each patient were preloaded with 15 mL/kg of Ringer's lactate solution before procedure.
- Pulse oximeter, noninvasive blood pressure monitoring and ECG were attached and baseline reading taken.

### Technique

- Under all strict aseptic and antiseptic precaution with patient in left lateral position, lumbar puncture was performed at L2-L3 intervertebral space with 23G Quincke's needle and selected drug was given slowly after free flow of clear CSF. After completion of procedure, patient was immediately turned to supine position.
- Pulse, BP, SPO<sub>2</sub> and RR were recorded Preoperatively and every 1, 5, 10, 15, 30, 45 and 60 minutes after giving spinal anaesthesia and then 1 hourly for 6 hours postoperatively.

### Evaluation

- The onset and duration of sensory blockade was assessed by using pinprick test every 1 minute till 15 minutes. Then, at 20, 30, 45 and 60 minutes and then every 30 minutes till completion of surgery.
- Time required for sensory block to reach level T10 dermatome level was considered as sensory onset.
- Motor blockade was assessed by modified Bromage score.
- Time for onset of grade 3 motor blockade was noted.
- After establishment of adequate level of block, surgery was started and time of beginning of surgery was noted.
- Intravenous fluid was administered depending on the weight of patient and adjusted according to surgery.
- Time for sensory regression to S1 dermatome level was noted.
- Time for motor regression to Bromage 0 was noted.
- The duration of effective analgesia was considered as time from intrathecal injection to administration of rescue analgesia.
- A VAS score of 4 was considered as time for regional anaesthesia and the time noted.
- Patients were watched for any intraoperative complications like bradycardia, hypotension, sedation, nausea, vomiting, dryness of mouth, pruritus and respiratory depression.
- Hypotension was defined as MAP >20% decrease from baseline value.
- Tachycardia was defined as heart rate >100/mins. and bradycardia was defined as heart rate <60/mins.

## RESULTS AND OBSERVATIONS

### Demographic Characteristics of the Patients in the Two Groups

Variables	No. of Patients	Mean	SD
Group M	50	43.72	9.66
Group N	50	40.79	10.45

**Table 1: Distribution of Age (in Years) between Two Groups**

$P = 0.1490$

Table 1 shows age distribution in each group. All the patients participating in the study were in age of 20 to 60 years. On statistical comparison using unpaired t test, P value was found to be >0.05. Hence, the two groups were comparable and non-significant.

Variables	No. of Patients	Male	Female	P value
Group M	50	18 (36%)	32 (64%)	0.42
Group N	50	15 (30%)	35 (70%)	

**Table 2: Sex Distribution**

Table 2 shows sex distribution of both the groups. 100 patients of either sex had participated in this study. Using chi-square test, both the groups were found to be comparable and non-significant.

Variables	No. of Patients	Mean	SD	P-value
Group M	50	155.04	6.20	0.39
Group N	50	154.11	4.5232	

**Table 3: Distribution of Height (in cm) in the Two Groups**

Table 3 shows distribution of height in each group. On statistical comparison using unpaired student's t test, the P value was found to be >0.05. Hence, the two groups were comparable and non-significant.

Variables	No. of Patients	Mean	SD	P-value
Group M	50	50.69	6.11	0.15
Group N	50	52.36	5.34	

**Table 4: Distribution of Body Weight (in Kilograms) in the Two Groups**

Table 4 shows distribution of body weight in each group. On statistical comparison, using unpaired student's t test, the

Variable	Group M (Mean±Standard Deviation)	Group N (Mean±Standard Deviation)	P value
Time to reach T10 sensory block (min.)	5.75±0.74	4.20±0.67	<0.0001
Time to reach highest level of sensory block (min.)	18.25±1.83	18.74±0.98	0.0991
Time to reach Bromage-3 (min.)	7.54±1.18	5.33±0.41	<0.0001
Regression time to S1 dermatome (min.)	199.44±10.41	154.84±8.11	<0.0001
Regression time to reach Bromage 0 (min.)	175.6±9.27	133.62±15.88	<0.0001
Time for rescue analgesia (min.)	241.06±19.6	257.30±28.50	0.0013

**Table 8: Comparison of Subarachnoid Block Characteristics between Magnesium and Nalbuphine Group**

Table 8 shows the onset time T10 sensory and motor blockade were significantly prolonged in Group M. Time for sensory and motor regression were prolonged in Group M, but duration of effective analgesia were prolonged in Nalbuphine group as compared to Magnesium group.

Adverse Effects	Groups	Incidence	P-value
Nausea	M	2 (4%)	>.05
	N	3 (6%)	
Vomiting	M	0	>.05
	N	1 (2%)	
Bradycardia	M	8 (16%)	>.05
	N	11 (22%)	

P value was found to be >0.05. Hence, two group were comparable and non-significant.

Variables	No. of Patients	ASA 1	ASA 2	P value
Group M	50	32 (64%)	18 (36%)	0.37
Group N	50	35 (70%)	15 (30%)	

**Table 5: Distribution of Patients in Groups According to ASA Physical Status 1 and 2 Status**

Table 5 shows distribution of patients in groups according to ASA 1 and 2. On statistical comparison using chi-square test, P value was found to be >0.05. Hence, the groups were comparable and non-significant.

Variables	No. of Patients	Mean	SD	P-value
Group M	50	70.33	11.12	0.36
Group N	50	68.05	13.80	

**Table 6: Comparison of Duration of Surgery (in min.)**

Table 6 shows distribution of duration of operation (in minutes) between the two groups. On statistical comparison using unpaired t test, P value was found to be >0.05. Hence, comparable and non-significant.

Proposed Surgery	Group M		Group N	
	No. of Patients	%	No. of Patients	%
Total abdominal hysterectomy	7	14%	10	20%
Vaginal hysterectomy	11	22%	8	16%
Herniorrhaphy	1	2%	6	12%
Hernioplasty	8	16%	4	8%
Haemorrhoidectomy	0	0	1	2%
Subtotal hysterectomy	2	4%	4	8%
Appendectomy	20	40%	17	34%

**Table 7: Comparison of Different Type of Operation**

P value=0.43 using chi-square test.

There is no significant difference in distribution of types of operation between the two groups.

Hypotension	M	11 (22%)	>.05
	N	13 (26%)	
Bradypnoea	M	0	>.05
	N	0	
Shivering	M	2 (4%)	>.05
	N	3 (6%)	
Pruritus	M	0	>.05
	N	0	
PDPH	M	0	>.05
	N	0	

**Table 9: Comparison of the Incidences of Adverse Effects between the Groups**

Table 9 adverse effect between two groups were comparable and statistically non-significant using Chi-Square Test.

## DISCUSSION

With more than 100 years of use, neuraxial anaesthesia has enjoyed much success and endured controversy. The ease of performance and versatility of spinal anaesthesia has resulted in its widespread popularity in both hospital and ambulatory surgical applications. Spinal anaesthesia is a safe and effective alternative to general anaesthesia when the surgical site is located on the lower extremities, perineum (e.g., surgery on the genitalia or anus), or lower abdominal wall (e.g., inguinal herniorrhaphy). Caesarean section deliveries are routinely performed under spinal anaesthesia as are total hip arthroplasty and total knee arthroplasty.

To improve the spinal anaesthetic efficacy, adjuvants from different pharmacological classes of drugs are used to enhance and prolong analgesia to lower-dose requirements and to reduce dose-dependent side effects of local anaesthetics. Opioids, first and foremost have attained an integral role as a spinal anaesthetic adjuvant.<sup>(7)</sup>

There are numerous experimental data that provide evidence that N-methyl-D-aspartate (NMDA) receptors play a significant role in neuronal plasticity and processes leading to central sensitisation to pain. NMDA antagonists have shown efficacy in the reduction of acute postoperative pain and analgesic consumption. Intrathecal Magnesium can be considered as a physiological blocker of NMDA receptors at dorsal horn thus preventing central sensitisation to pain. There are studies where Magnesium has been administered by different routes such as intravenous, intrathecal, or via epidural that improved anaesthetic and analgesic quality.<sup>(8)</sup> In the present study, we compared the effect of addition of intrathecal Nalbuphine and intrathecal Magnesium sulfate to bupivacaine spinal block. The onset of T10 sensory block 5.75±0.74 min. in group M and 4.20±0.67 min. in group N, which is significantly faster in Nalbuphine group ( $p < 0.0001$ ). Time of regression to S1 sensory level is 199.44±10.41 min. in group M and 154.84±8.11 min. in group N. The sensory regression time is significantly prolonged in magnesium group ( $p < 0.0001$ ).

The characteristic of sensory block in our study is more or less similar to other studies with intrathecal Nalbuphine or magnesium sulfate when used as adjuvants with intrathecal bupivacaine in spinal anaesthesia. Ozalevli et al<sup>(9)</sup> observed similar delay in onset of T<sub>10</sub> sensory analgesia on addition of Magnesium sulfate in Bupivacaine-fentanyl spinal anaesthesia. Sunil BV et al<sup>(10)</sup> in 2013 in his study found similar delay in onset of sensory block 6.46±1.32 minutes. He also observed the Sensory regression time in Magnesium group is (236.6±34.5) minutes, which is slightly prolonged than our studies. Marzieh-Beigom Khezri et al<sup>(11)</sup> in 2011 conducted study on 90 patients undergoing lower limb orthopaedic surgery. Patient in magnesium group received 3 mL of 0.5% bupivacaine plus 0.5 mL of 10% magnesium sulfate. The T<sub>10</sub> sensory onset in Magnesium group is 5.86±1.25 min., which is comparable with our studies, sensory regression time 132.06±11.47 min. in Magnesium group and the sensory regression is quicker than our study. Dr. Charu J. Pandya et al<sup>(12)</sup> in 2013 conducted study on 60 patients undergoing lower abdominal study. They were divided into two groups of

30 each. Both group received drugs similar to our study. Onset of T<sub>10</sub> sensory block is 5.1±0.8 minutes in Magnesium group. The results were comparable with our study. Sensory regression is also similar to our study.

Jyothi B et al<sup>(13)</sup> in 2014 conducted a study on 100 patients undergoing lower limb and lower abdominal surgeries, they were divided into four groups A, B, C, D; each group receiving 3 mL of 0.5% heavy bupivacaine with 0.5 mL of normal saline, 0.8 mg, 1.6 mg and 2.4 mg Nalbuphine with normal saline (total volume 3.5 mL), respectively, injected intrathecally. The time to onset of sensory blockade in the group injected with 0.8 mg of Nalbuphine was found to be 3.3±0.8 min., which was comparable with our study. In a study conducted by Gomaa et al in 2014,<sup>(14)</sup> comparing 0.5 mL of 2 mcg fentanyl with 0.5 mL of 0.8 mg nalbuphine with 2 mL of 0.5% hyperbaric bupivacaine. The time of onset of sensory block was found to be 1.64±0.09 min. and 1.60±0.10 min., respectively. The difference in the results with our study may be attributed to difference in the demographic profile of the patients selected for the study. The type of operation conducted (caesarean section) as well as the different drug dosage used keeping in mind the demography of the patients. In a study conducted by Mukherjee et al in 2011<sup>(15)</sup> with 0.8 mg intrathecal Nalbuphine, the time for sensory regression to S1 was found to be 153.3±6.05 min. In another study conducted by HM Gomaa et al in 2014,<sup>(14)</sup> the time for sensory regression to S1 was 123.00±5.66 min. While Patwa et al<sup>(16)</sup> found the sensory regression to S1 to be 98.16±9.86 min. after injecting 0.5% 15 mg heavy bupivacaine (3 mL) with 1 mg of Nalbuphine (0.5 mL).

In our study, onset of Bromage grade 3 motor blockade 7.54±1.18 min. in magnesium group and 5.33±0.41 in Nalbuphine group, regression of motor blockade 175.6±9.27 min. in magnesium group while 133.62±15.88 in Nalbuphine group. In a study conducted by Dr. Charu J. Pandya et al<sup>(12)</sup> with intrathecal Magnesium Sulfate, the onset of Bromage grade 3 motor block is 7±1 minutes and Bupivacaine group was 5.2±0.8 minutes. Alem Wapang et al<sup>(17)</sup> in another study with intrathecal Magnesium sulfate found that onset of Bromage grade 3 motor block in Magnesium group was 8.00±1.29 min. Sunil BV<sup>(10)</sup> et al in another study found the onset of Bromage 3 motor block to be 7.28±1.21 minutes. The result of these studies were comparable with our study. Dr. Charu J. Pandya et al<sup>(12)</sup> found the regression time to Bromage 0 was 175.25±7.69 minutes. Alem Wapang et al<sup>(17)</sup> found the regression time to Bromage 0 156.50±12.26 minutes. The result of the above-mentioned studies were comparable with our study. In another study Marzieh-Beigom Khezri et al<sup>(11)</sup> found motor regression time to Bromage 0 was 118±14.65 minutes, which is significantly less than our study.

In a study conducted by H. M. Gomaa et al<sup>(14)</sup> with intrathecal Nalbuphine, the time of onset of grade III motor blockade was found to be 5.72±0.17 minutes. Similarly, in studies conducted by Mukherjee et al,<sup>(15)</sup> Sagar et al,<sup>(18)</sup> Shakoo et al,<sup>(19)</sup> the time of onset of grade III motor blockade was found to be 5.6±0.53 minutes, 5.9±0.4 minutes and 4.47±1.46 minutes, respectively. In studies conducted by Mukherjee et al,<sup>(15)</sup> H.M Gomaa et al,<sup>(14)</sup> Sagar et al,<sup>(18)</sup> the duration of motor blockade was found to be 141.0±5.83 minutes, 125.33±5.71 minutes and 142.2±6.7 minutes respectively, which are comparable with our observation.

In our study, no patients required additional analgesics intraoperatively. Postoperative pain was assessed using a 10 cm Visual Analogue Scale (VAS) where '0' indicated 'No Pain' and '10' indicated 'worst imaginable pain'. The VAS score was recorded immediate postoperative 0 hrs. and at 1 hrs., 2 hrs., 3 hrs., 4hrs., 5 hrs., 6 hrs. postoperatively. The mean time for rescue analgesia in Bupivacaine Magnesium group is  $241.06 \pm 19.61$  minutes and nalbuphine group is  $257.30 \pm 28.50$  min., which is statistically significant ( $P$  value=0.0013) Dr. Suhrita Paul et al<sup>(20)</sup> Marzieh-Beigom.

Khezri et al,<sup>11</sup> M.P. Nath et al<sup>(21)</sup> 2012 found duration of effective analgesia with magnesium  $382.13 \pm 46.9$  minutes,  $318.33 \pm 74.62$  minutes and  $291.4 \pm 18.6$  minutes respectively. The duration is significantly more than our studies and the results may be attributed to different demographical profile of the patients. The duration of effective analgesia in our study is comparable with the studies of Dr. Charu J. Pandya<sup>(12)</sup> et al, Alem Wapang et al.<sup>(17)</sup>

HM Gomaa et al,<sup>14</sup> Mukherjee et al,<sup>15</sup> Shakooch et al,<sup>19</sup> Sagar et al<sup>18</sup> and Patwa et al<sup>16</sup> found the duration of analgesia in patients injected with intrathecal Nalbuphine to be  $231.83 \pm 15.73$  minutes,  $278.5 \pm 6.04$  minutes,  $298.0 \pm 51.02$  minutes,  $270.0 \pm 27.4$  minutes and  $302.4 \pm 27.59$  minutes, respectively. They used 0.4 mg to 1 mg Nalbuphine intrathecally. The finding are comparable with our studies.

## CONCLUSION

Nalbuphine has faster onset of anaesthesia and provides prolonged postoperative analgesia compared to magnesium sulphate when used as adjuvants with Bupivacaine in spinal anaesthesia.

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