

# The Analgesic Efficacy of Intrathecal Bupivacaine and Fentanyl with Added Neostigmine or Magnesium Sulphate

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## Abstract

**Background:** An appropriate anesthesia duration with minimal side effects and prolonged postoperative analgesia are the ideal characteristics of an intrathecal drug used during spinal anesthesia. Neostigmine and magnesium sulphate have been used as spinal anesthetic additives with narcotics and local anesthetics.

**Objectives:** This study aimed to assess the analgesic properties of intrathecal neostigmine and magnesium sulphate by adding them to intrathecal bupivacaine-fentanyl.

**Methods:** In total, 210 patients undergoing tibial fracture surgery were enrolled in a double-blinded clinical trial study. Patients were randomly allocated to one of three groups: group F received 10 mg of bupivacaine and 25  $\mu$ g of fentanyl as intrathecal drug for spinal anesthesia, group N received 150  $\mu$ g of neostigmine added to 10 mg of bupivacaine and 25  $\mu$ g of fentanyl, and group M received 50 mg of magnesium sulphate added to 10 mg of bupivacaine and 25  $\mu$ g of fentanyl. Analgesia duration, motor blockade scores, postoperative pain scores 6 and 12 hours after surgery, postoperative voiding time, and the incidence of hypotension, bradycardia, respiratory depression, and nausea and vomiting were recorded.

**Results:** Group M showed significantly longer analgesia duration ( $330.76 \pm 80.98$  minutes) than group F ( $280.98 \pm 60.33$  minutes). The pain scores in group M 6 hours (NRS:  $2.44 \pm 0.98$ ) and 12 hours (NRS:  $4.10 \pm 0.88$ ) after surgery were significantly lower than those of the other two groups. Before discharge from recovery, motor blockade scores and voiding time were not significantly different between the three groups. Hypotension (40%), bradycardia (25%), and nausea and vomiting (70%) were more obvious among group N patients. Respiratory depression did not occur in any patients.

**Conclusions:** The addition of 50 mg of magnesium sulfate to a bupivacaine-fentanyl solution for intrathecal anesthesia improved the efficacy and duration of the analgesia without any significant side effects. The addition of 150  $\mu$ g of neostigmine increased the incidence of hypotension, bradycardia, and nausea and vomiting. Moreover, neostigmine failed to prolong analgesia duration.

**Keywords:** Intrathecal Injection, Neostigmine, Magnesium Sulphate

## 1. Background

Neuraxial anesthesia is a preferred anesthesia method for some patients due to the reduction of drug administration and side effects, the potential for better anesthesia management in patients with concurrent diseases, and faster recovery and discharge. Regional and neuraxial anesthesia can also reduce postoperative pain more efficiently than oral or parenteral analgesics, can diminish admission time, and can restore a patient's movement and bowel function shortly after anesthesia (1-4).

Bupivacaine with long-term analgesia is a suitable choice for spinal anesthesia (5). Fentanyl has an impressive profile for neuraxial anesthesia, having rapid clearance from the CSF, high lipid solubility, and minimal upward expansion. Therefore, complications, such as delayed respiratory depression, occur less frequently with fentanyl (6). Other opioids, such as pethidine, have been used successfully in combination with local anesthetics for spinal anes-

thesia (7, 8). Adjuvant spinal drugs, such as epinephrine, clonidine, and neostigmine, can increase the duration and potency of spinal anesthesia (8).

Magnesium sulfate noncompetitively blocks N-methyl aspartate (NMDA) receptors. Therefore, the central sensitization and activity of excitatory amino acids, such as glutamate and aspartate in the posterior horn, would be blocked efficiently (9). Magnesium is a physiologic calcium antagonist and a calcium reuptake regulator for cells (10).

Neostigmine is an acetyl cholinesterase inhibitor, and in the subarachnoid space, neostigmine increases acetylcholine concentration and induces analgesia. Furthermore, neostigmine potentiates analgesia by releasing nitric oxide in the spinal cord (11). Acetylcholine inhibits afferent pain impulses to lamina 1, 2 and 3 of the dorsal horn through M1 and M2 muscarinic receptors (12). Intrathecal neostigmine has dose-dependent complications, such as

nausea, vomiting, sedation, muscle weakness, and sometimes temporary reduction of tendon reflexes.

Other drugs have been tried as adjuvants to spinal drugs in animal models (13).

## 2. Objectives

In this study, we compared the duration, quality of analgesia, and side effects of spinal anesthesia induced by intrathecal bupivacaine and fentanyl with either neostigmine or magnesium sulfate for tibial fracture patients.

## 3. Methods

In total, 70 patients with an ASA class I or II tibial fracture who were 18 - 40 years old, who had no absolute or relative contraindication for spinal anesthesia, and who had no drug abuse history were randomly enrolled in one of three groups after giving informed consent to participate in this study.

Group F received 25  $\mu$ g of fentanyl (Caspian, 50  $\mu$ g/mL) with 10 mg of bupivacaine (Merck, 0.5%) intrathecally. Group N received 150  $\mu$ g of neostigmine (Caspian, 0.5 mg/mL) in addition to the 25  $\mu$ g of fentanyl and 10 mg of bupivacaine administered to group F. Group M received 50 mg of magnesium sulfate (Ghazi, preservative-free vial, 50%) in addition to the 25  $\mu$ g of fentanyl and 10 mg of bupivacaine.

Blood pressure and heart rate, the duration of analgesia after the spinal procedure, the degree of motor block before discharge from recovery, pain scores at 6 and 12 hours after the surgery, and the first post procedure voiding time were recorded.

Information was analyzed using SPSS software version 17. For analgesic duration and pain scores, variance analysis and Tukey's test were used, and for other qualitative variables, a chi-squared test was employed.

All patients were enrolled in the double-blinded clinical trial and were randomly allocated to one of the three groups using a three-block randomization method. After volume expansion with 5 cc/kg of intravenous normal saline, spinal anesthesia was performed with the patient in a lateral decubitus position under sterile conditions in the L4-L5 or L3-L4 interlaminar space with a 25-gauge Quincke spinal needle.

Drugs were injected after observing the free flow of the CSF. The onset and level of anesthesia were evaluated by wet cotton, and patients with a sufficient level of anesthesia were enrolled in the study.

The patients' pain scores were recorded every 20 minutes during surgery, and a score of 3 or more on the NRS

scale represented spinal analgesia termination. Any incidence of nausea and vomiting or hypotension and bradycardia was recorded and treated properly. Motor block levels were measured using the Bromage scale before each patient was discharged from recovery. On this scale, the first degree represented no blockage in the motor function of the lower extremities, the second degree represented a patient's ability to bend the knee to a minimal degree with preserved feet movement, the third degree represented only feet movement, and the fourth degree represented complete blockage of the lower limbs.

The first postoperative voiding time was recorded, and pain scores in the ward were recorded 6 and 12 hours after surgery.

## 4. Results

In this study, 210 patients, including 120 males (57%) and 90 females (43%) with a mean age of  $27.9 \pm 5.74$  years underwent the surgery. There was no significant sex difference among the three groups ( $P > 0.05$ ). The mean age of group F ( $27.92 \pm 5.74$  years old) was greater than that of group N ( $26.17 \pm 4.97$  years old) and group M ( $25.16 \pm 4.76$  years old), but the difference in age between groups was not significant ( $P = 0.73$ ).

Table 1 presents the mean duration of analgesia. The differences between groups F and N and groups M and N were not significant ( $P > 0.05$ ), but a significant difference was seen between groups F and M.

**Table 1.** Distribution of Analgesia Time in the Studied Groups

Group	Analgesia Duration, Min	P Value
F	$280.98 \pm 60.33$	Not significant
N	$300.68 \pm 83.54$	Not significant
M	$330.76 \pm 80.90$	0.04

The average vomiting time was  $21.87 \pm 10.1$  minutes after anesthesia.

In total, 50 patients experienced nausea (24%), and 70% of these patients belonged to group N, 17% belonged to group M, and 13% belonged to group F. The difference in the number of patients who experienced nausea between Group N and the other two groups was significant ( $P = 0.001$ ), but this difference was not significant between groups F and M ( $P > 0.05$ ).

Hypotension occurred in 66 cases (31.5%); it occurred in 40% of patients in group N, 30% of patients in group M, and 24% of patients in group F. The difference in the number of patients who experienced hypotension between Group N and the other two groups was significant ( $P = 0.04$ ), but

this difference was not significant between groups F and M ( $P > 0.05$ ).

Bradycardia was detected in 35 patients (16%). This event occurred in 25% of group N patients, 15% of group F patients, and 10% of group M patients. The difference in the incidence of bradycardia between Group N and the other two groups was significant ( $P = 0.38$ ) and ( $P = 0.043$ ), but this difference was not significant between groups F and M ( $P > 0.05$ ).

NRS scores were significantly lower for the patients of Group M 6-12 hours after the operation than the other two groups ( $P = 0.032$ ) (Table 2).

**Table 2.** Mean and Standard Deviation of NRS Scores in the Studied Groups

Group	NRS 6 Hours After Surgery	NRS 12 Hours After Surgery	P Value
F	5.13 ± 1.32	6.97 ± 1.08	Not significant
N	4.54 ± 1.12	6.00 ± 1.15	Not significant
M	2.44 ± 0.98	4.10 ± 0.88	0.032

The mean motor block score before discharge from recovery was  $2.55 \pm 0.68$ , and the differences between these scores for the three groups was not significant ( $P > 0.05$ ) (Table 3).

**Table 3.** Motor Block at the Time of Discharge from Recovery

Group	Mean and Standard Deviation of Bromage Scale Scores	P Value
F	2.00 ± 0.55	Not significant
N	2.66 ± 0.34	
M	3.15 ± 0.85	

The mean voiding time after spinal anesthesia was  $397.02 \pm 24.40$  minutes, and the difference in this time between the groups was not significant ( $P > 0.05$ ).

## 5. Discussion

Spinal anesthesia has a more rapid onset and is a more reliable analgesia than other regional anesthesia techniques. The disadvantages of spinal anesthesia are a high incidence of cardiovascular instability and a short duration of analgesia. Therefore, adjunctive medications for intrathecal anesthesia have been used to intensify spinal anesthesia with minimal complications (14).

In our study, the mean duration of analgesia in group M, which received fentanyl, bupivacaine, and magnesium

sulfate, was longer than the other two groups. This finding was comparable to previous studies. The intrathecal injection of magnesium sulfate potentiates NMDA receptor blocking in the spinal cord and increases the duration and quality of analgesia to diminish postoperative analgesic consumption (15-17). Additionally, previous studies have not revealed any specific side effect of magnesium sulfate (15-18).

Postoperative pain management is a great concern for the inhibition of central sensitization and the prevention of chronic pain (19, 20). NRS scores were significantly lower in group M than in the other two groups 6 and 12 hours after operation, which can be attributed to magnesium sulfate.

The incidence of nausea and vomiting was lower in group M than in group N but was similar in groups M and F. Additionally; the incidence of hypotension in group M was lower than in the other two groups. The incidence of nausea and vomiting and the incidence of hypotension were very similar in groups M and F, which indicates that magnesium sulfate did not increase the occurrence of these complications.

Intrathecal neostigmine considerably increases the incidence of nausea and vomiting (14, 21). Nausea is a dose-dependent complication. The maximum neostigmine dose that can be given without increasing the incidence of nausea employed in previous studies was  $150 \mu\text{g}$ , but this dose obviously increased the incidence of nausea in the patients in our study.

One potential complication of spinal anesthesia is urinary retention, which can postpone discharge time. According to this study, neostigmine or magnesium sulfate as the third component of the bupivacaine-fentanyl intrathecal drug combination did not prolong recovery time or voiding retardation.

Motor block and recovery discharge time were not significantly different between groups (16). Adding magnesium sulfate or neostigmine did not cause any delay in motor recovery and discharge. Adding magnesium sulfate to intrathecal bupivacaine-fentanyl in this study did not prolong the motor block of the lower extremities or recovery time, which may be related to the lower dose of magnesium sulfate used in this study compared with previous trials. This event requires further evaluation with various doses.

## Footnote

**Authors' Contribution:** Study concept and design: Mehrdad Mokaram and Farid Foruzin; analysis and interpretation of data: Farid Foruzin; drafting of the manuscript: Mehrdad Mokaram; critical revision of the

manuscript for important intellectual content: Mehrdad Mokaram; statistical analysis: Farid Foruzin.

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