Anesthetic effects of adding intrathecal neostigmine or magnesium sulphate to bupivacaine in patients under lower extremities surgeries

Seyed Hamid Reza Faiz, Poupak Rahimzadeh, Mozhgan Sakhaei[1], Farnad Imani[2], Pooya Derakhshan[3]

Assistant Professor of Anesthesiology and Pain, Tehran University of Medical sciences, [1]Anesthesiologist, [2]Associate Professor of Anesthesiology and Pain, Tehran University of Medical sciences, [3]Assistant Professor of anesthesiology, Birjand University of Medical Sciences

Background: Regional anesthesia is widely used to perform different surgical procedures including those performed on the extremities. In this study, the anesthetic effects of adding intrathecal neostigmine or magnesium sulphate to bupivacaine in patients under lower extremities surgeries were assessed. **Materials and Methods:** In this double-blind randomized clinical trial, 90 patients, candidate for lower extremities surgeries in a training hospital, were recruited. The patients with ASA class I and II aging from 20 to 65 years between 2009 and 2010 were evaluated. The selected patients were randomly assigned to receive either bupivacaine alone (Group A, $n=30$), or bupivacaine plus magnesium sulphate 50% (Group B, $n=30$), or bupivacaine plus neostigmine (Group C, $n=30$). Then sensory and motor onset and complete block and the time of recovery were measured. **Results:** The sensory block onset time were 3.03 ± 0.981 in group A, 3.90 ± 2.71 in group B and 3.7 ± 1.08 in group C and knee flexion time were not significantly different among the three groups ($P > 0.05$), whereas the time to complete motor block was significantly longer in group C and motor recovery time were significantly different between groups ($P=0.001$). **Conclusions:** According to the obtained results, it may be concluded that magnesium sulphate is a safe and effective adjuvant for increasing the onset time of motor block.

Key words: Bupivacaine, magnesium sulphate, motor block, neostigmine, sensory block, spinal anesthesia

INTRODUCTION

Regional anesthesia is widely used to let the performance of different surgical procedures including those performed on the extremities.[1] Previous studies have demonstrated that both spinal and epidural anesthesia tend to have reduced blood loss and rates of Deep Venous Thrombosis (DVT), less general anesthesia induced adverse effects such as nausea, sore throat, alteration of mental status, and cognitive dysfunction, and allowing an improved pain control.[2-5]

Regional anesthetic techniques may lead to blockade or reduced pain ranged from several hours to several days.[1] Better pain control may result in an earlier hospital discharge and may improve the patient's ability in postoperative period.[6] In addition, it is usually easy to administer and readily available.[7]

It has become a common practice to use different therapeutic regimens for treating intra and postoperative pain and increasing the regional anesthetic period, because no drug has yet been identified to have this advantage without associated therapeutic side effects. [1,8] One method to increase the duration and reduce side effects is to administer combinations of other classes of analgesics with local anesthetics. One such class is Neostigmine a cholinergic drug, because acetylcholine produces analgesia by a spinal mechanism. In auto radiographic studies muscarinic receptors have found in lamina II and III of spine, Which can be influenced by neostigmine. Intrathecal neostigmine produces some analgesia alone, but with delay. Dose-dependent nausea has also been observed.

Spinal neostigmine alone produces analgesia in humans and animals at doses greater than 100 μg.[9-11] We chose

Access this article online	
Quick Response Code:	**Website:** www.journals.mui.ac.ir/jrms
	DOI: ***

a dose of 25 µg because this dose would be unlikely to cause side effects and has produced evidence of analgesia in clinical trials.[9,10]

Additionally, spinal neostigmine has been associated with a reduction in the dose of spinal narcotics required to produce postoperative analgesia.[10,11]

Because magnesium is a noncompetitive antagonist to NMDA receptors, it has the potential to prevent central sensitization from peripheral nociceptive stimulation. In previous studies, it was demonstrated that intrathecally administered magnesium prolonged spinal opioid analgesia, both in rats and humans.[12,13] The addition of intrathecal magnesium to spinal anesthesia improved postoperative analgesia in an orthopedic setting.[13,14]

Due to the fact that both neostigmine and magnesium sulphate have shown effects on local anesthetic effects, we considered these two drugs and compared their equivalent doses effects as an adjuvant. Because the effects of adding these two non-opioid drugs in such a concentration and comparing their effects have not studied formerly.

The purpose of this study was to assess the anesthetic effects of adjuvant therapies with neostigmine or magnesium sulphate compared with bupivacaine alone in patients under lower extremities surgeries with spinal anesthesia.

MATERIALS AND METHODS

In this double-blind randomized clinical trial, After review the literature we found that with α=0.05 and β=0.1 and 90% power and δ=8.5 and σ =10 minutes, the sample size was calculated from the below formula:

$$2N = \frac{4(Z\alpha + Z\beta)^2 \sigma^2}{\delta^2}$$

N=30 in each group was found, So 90 ASA I and II patients, candidate for lower extremities surgeries aging from 20 to 65 years in a training hospital from 2009 to 2010, were recruited. Informed consent was obtained. The study was approved by the Tehran University of Medical Sciences Ethics Committee and was performed in accordance with the Declaration of Helsinki. The inclusion criteria were patients between 20-65 years who were candidates for lower extremity surgeries. The exclusion criteria were contraindications for regional anesthesia including local infection, hemorrhagic disorders, drug hypersensitivity, muscular disorders and central and peripheral neuropathy, and drug abuse history and addiction.

The selected patients were randomly assigned (in a block random manner) to receive either bupivacaine 0.5% Spinal heavy 4 cc (Astra Levent- Zeneca, Istanbul, Turkey) alone (Group A, *n*=30), or bupivacaine plus magnesium sulphate 50% (Pasteur Institute, Tehran, Iran) (Group B, *n*=30), or bupivacaine plus neostigmine 0.5 mg/ml (1 ml) (Caspian Tamin Co. Rasht, Iran) (Group C, *n*=30). The anesthesiologist in the operation room had no information about the prepared drugs for the patients and it was made in similar syringes by another colleague. The age, sex, ASA class, duration of surgery, sensory and motor function, hemodynamic status (systolic and diastolic blood pressures, heart rate, and SPO2), drug side effects, and recovery time were under-study variables and recorded by anesthesiologist who were unaware of the group. The patient and the anesthesiologist were blinded for the groups [Figure 1].

The standard monitoring included ECG, pulse oximetry and NIBP. After IV line was prepared with catheter 18, 15 cc/kg normal saline was infused to all patients with no premedication given. The patients were in lateral standard position and the foot was in dependent position. Lumbar puncture after subcutaneous injection of 2 cc lidocaine 0.5% in L3-L4 level from midline approach with a 25G in 90 mm needle was performed (Dr. Japan Co. LTD -K-3 point type).

After the CSF flow was seen, all patients received 3 cc bupivacaine 0.5% (15 mg) and then another blinded person prescribed the above-mentioned drugs to each group. The 50 mg magnesium sulphate was prepared by 1 cc of magnesium sulphate 50% plus 9 cc normal saline 0.9% and the 25 microgram neostigmine was prepared with 1 cc of neostigmine 0.5% plus 19 cc normal saline 0.9%.

After intrathecal injection, the patient was repositioned as supine. Then bilateral sensory and motor block after the injection and each min then to rise to T10 level, were evaluated and recorded by a blinded observer. Also the heart rate, respiratory rate, SPO2, and systolic and diastolic blood pressures were recorded 5 min before and then each 15 min up to the end of the surgery.

The sensory block onset, top level of sensory block, motor block onset, and the completion of motor block and recovery were recorded. The sensory block onset was defined as time from intrathecal injection to lack of pain in T10 level with pin prick test.

Top level of sensory block was evaluated using pin prick test every 5 to 25 min after intrathecal injection. The motor block was evaluated by Modified Bromage Scale as below:[14,15]
0: Without motor block
1: Impossibility of hip flexion

2: Impossibility of knee flexion

3: Impossibility of ankle flexion

Motor block onset was defined as the time from intrathecal injection to impossibility of knee flexion. Also the complete motor block was defined as impossibility of ankle flexion.[14,15] When the score was zero in Bromage classification, it was considered as recovery from complete motor block.[14,15] Also the intra-operative and recovery phase complications including nausea and vomiting, itching, dyspnea, respiratory rate less than 10 per min, hypoxia, bradycardia, and hypotension were recorded. If the blood pressure was reduced to less than 90 mmHg, 10 mg IV ephedrine was injected and if the heart rate was reduced to less than 45 beats per min, 0.5 mg IV atropine was injected. After relief of motor and sensory block, the patients were discharged from recovery room to the ward.

Data from 90 patients were analyzed using SPSS (version 18.0) software (Statistical Procedures for Social Sciences; Chicago, Illinois, USA). Differences were tested by Independent-Sample T and Chi-Square tests and were considered statistically significant at *P* values less than 0.05.

RESULTS

The mean ages in groups A, B, and C were 34.57 ± 17.45, 34.07 ± 12.27, and 33.33 ± 14.76 years, respectively (*P*=0.950). Thirty subjects (100%) in group A, 23 patients (76.7%) in group B, and 24 patients (80%) in group C were male (*P*=0.021). The mean duration of surgery in groups A, B, and C were 117.48 ± 40.26, 98.39 ± 37.66, and 111.88 ± 41.01 min, respectively (*P*=0.184).

The sensory block onset time and motor block onset time (knee flexion time) were not significantly different among the three groups (*P* > 0.05), whereas the time to complete motor block was significantly longer in Group C and motor block recovery time were significantly different among groups (*P*=0.001) [Table 1]. The anesthesia levels were T4 in 5 patients, T6 in 21 patients, and T8 in four patients in group A. T4 in 19 subjects, T6 in 8 patients, T8 in one subject, and T10 in 2 patients in group B. The anesthesia levels were
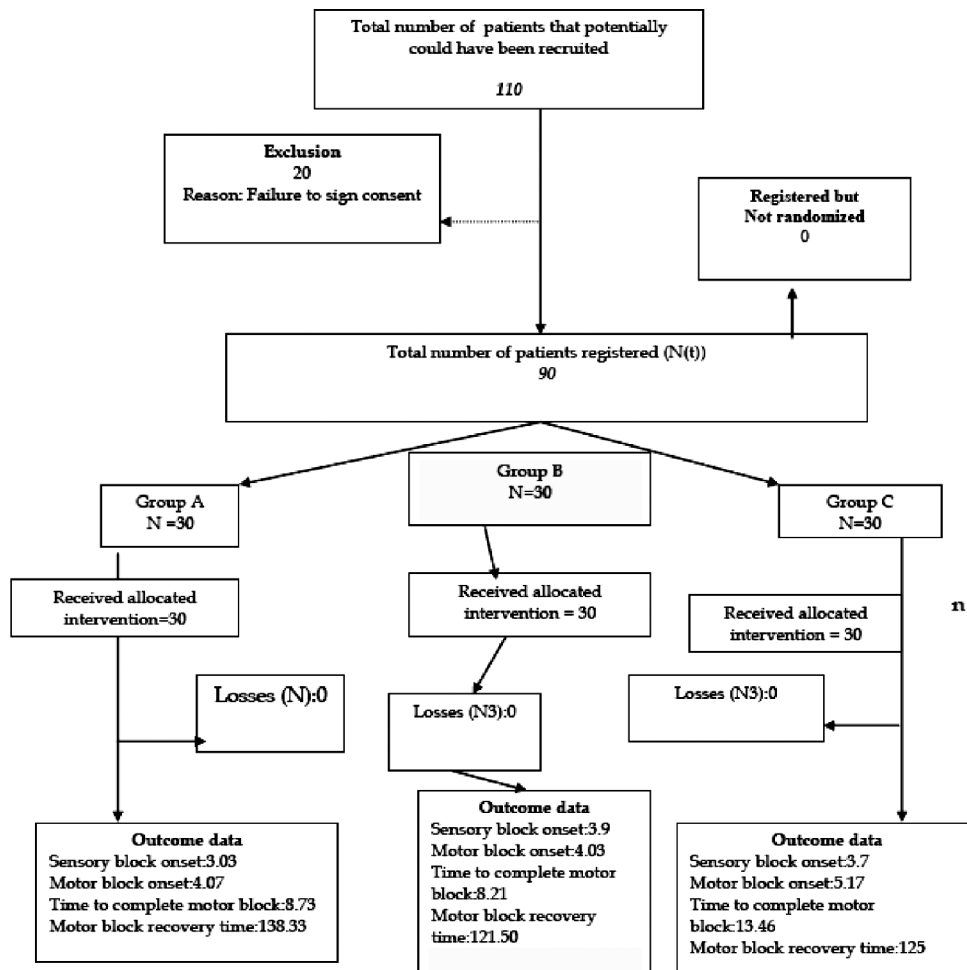

Figure 1: Flowchart of Subject Enrollment

| October 2012 |
Journal of Research in Medical Sciences
www.mui.ac.ir
920

Table 1: Sensory and motor response in the three studied groups

Group		Sensory block onset time	Motor block Onset time	Time to complete Motor block	Motor block Recovery time
Bupivacaine (G1)	Mean	3.03	4.07	8.73	138.33
	Std. Deviation	0.981	1.964	4.719	30.267
Bupivacaine+Magnesium (G2)	Mean	3.90	4.03	8.21	121.50
	Std. Deviation	2.771	2.025	6.472	21.701
Bupivacaine+Neostigmine (G3)	Mean	3.70	5.17	13.47	125.00
	Std. Deviation	1.088	3.041	5.309	27.418
P-value		*P*>0.05	*P*>0.05	*P*=0.001	*P*=0.001

T4 in 15 subjects, T6 in 10 patients and T8 in 5 subjects in group C without any significant differences ($P > 0.05$).

The drug-related adverse effects were as follows: four subjects (13.3%) in group A (two cases of nausea and two cases of itching), two patients (3.3%) in group B (one case of nausea and one case of itching), and 13 patients (30%) in group C (intraoperative nausea in three subjects, and nausea in seven patients in recovery and vomiting in recovery in three patients) (P=0.016), Which was statistically meaningful The homodynamic status was not significantly different across the study among the three groups ($P > 0.05$).

DISCUSSION

Our results showed that the time to complete motor block and motor recovery time were significantly different among the three studied groups and were shorter in the magnesium group. Also, the patients in the magnesium group experienced less therapeutic side effects compared with the other groups in a significant manner.

In a study by Ghatak *et al.*, in 2010 in India, the onset of anesthesia was faster in magnesium group which was not similar with our research results.[15] In the Ghatak *et al.*, study, the groups were similar with respect to hemodynamic status, nausea and vomiting; but our study showed that only hemodynamic status was similar and the other side effects were less common in those patients who received bupivacaine plus magnesium sulphate.

Central sensitization is an activity-dependent increase in the excitability of spinal neurons and is considered to be one of the mechanisms implicated in the persistence of postoperative pain.[15] Central sensitization has been shown to depend on the activation of dorsal horn *N*-methyl-D aspartate (NMDA) receptors by excitatory amino acid transmitters such as aspartate and glutamate.[12,13] In a previous study, adding a low dose of ketamine (0.15 mg·kg–1, i.v.), a noncompetitive antagonist of NMDA receptors, to a multimodal analgesic regimen improved postoperative analgesia and functional outcome.[12,13] In this study, Magnesium sulphate was used for the above

mentioned reason and showed that faster block onset and recovery could be achievable with this drug.

Taheri *et al.*, performed a study in Iran and found that duration of analgesia was longer in patients who received bupivacaine plus tramadol compared with bupivacaine plus neostigmine. There were no significant differences in heart rate, mean arterial pressure, and oxygen saturation between groups, as well as our study. Adverse effects excluding the vomiting were not observed in any patients in their study, whereas in our study there were two cases of itching.[16]

In another study performed by D'Angelo *et al.*, in 2001 in the United States, the spinal neostigmine produced severe nausea and did not significantly increase the duration of spinal analgesia compared with bupivacaine, an observation which was similar to our findings in the current study showing more adverse effects in the neostigmine group.[17]

Spinal neostigmine alone uniformly produces analgesia in large doses (100–200 μg), but it also results in significant dose-dependent nausea. Nausea associated with spinal neostigmine is thought to result from spread in CSF to brainstem sites and is not responsive to standard antiemetics. The incidence of nausea can be reduced in volunteers with the addition of glucose to the neostigmine solution, especially in lateral position and with lower volume of inject ate.[10,11] In our study we had nausea and vomiting in 30% of the patients with the used dosage.

In Dayioglu *et al.*, study in Turkey, the addition of intrathecal magnesium to spinal anesthesia by bupivacaine prolonged the time for recovery from anesthesia, but did not affect the time to reach the highest level of sensory block similar to our study. Also, the mean times to complete recovery of motor function were similar in the two groups. This was not similar to our findings in this study.[18]

Unlugenc *et al*, showed that the addition of magnesium sulfate to bupivacaine did not shorten the onset time of sensory and motor blockade or prolong the duration of spinal anesthesia. Similar observations were made in our study for the sensory blockade time.[19] In a study by

Ozalevli *et al.*, in Turkey, it was observed that in patients undergoing lower extremity surgery, the addition of magnesium sulphate to spinal anesthesia induced by bupivacaine and fentanyl significantly delayed the onset of both sensory and motor blockade, but also prolonged the period of anesthesia without additional side-effects.[20] These findings were in somehow in accordance with our results in the current study. Finding the longer onset time was an finding and was not our goal. We believe that it is not a favorite effect for starting a surgery but in this study we found this unpleasant effect.

In summary, according to the obtained results, it may be concluded that the magnesium sulphate is a safe and effective adjuvant therapeutic for enhancing onset time of motor block. Accordingly, use of magnesium sulphate for regional anesthesia may be considered on the bases of the patients' condition and physician's opinion. While as our findings showed that neostigmine could prolong the onset time and it should be considered since usage especially in urgent cases need faster anesthesia.

It has been advocated by the writers of the article to perform more researches with different magnesium and neostigmine dosage in more patients in different procedure settings in the future to find more details about the safest route and dosage.

Our study has the limitation of only one dose-response evaluation. We preferred to use a smaller dose of magnesium and neostigmine that would not cause any side-effects.

ACKNOWLEDGMENTS

REFERENCES

1. Breivik H, Norum HM. Regional analgesia--risks and benefits. Tidsskr Nor Laegeforen 2010;130:392-7.
2. Chelly JE, Ben-David B, Williams BA, Kentor ML. Anesthesia and postoperative analgesia: Outcomes following orthopedic surgery. Orthopedics 2003;26:S865-71.
3. Flood BM, Shah MV. Intravenous regional anaesthesia for lower limb orthopaedic surgery. Ann R Coll Surg Engl 1988;70:257.
4. Reilley TE, Terebuh VD, Gerhardt MA. Regional anesthesia techniques for the lower extremity. Foot Ankle Clin 2004;9:349-72.
5. Tziavrangos E, Schug SA. Regional anaesthesia and perioperative outcome. Curr Opin Anaesthesiol 2006;19:521-5.
6. Kirkebøen KA, Lindholm E, Raeder J. Choice of anaesthetic approach and anaesthetic drugs. Tidsskr Nor Laegeforen 2010;130:388-91.
7. Buist RJ. A survey of the practice of regional anaesthesia. J R Soc Med. 1990;83:709-12.
8. Eledjam JJ, de La Coussaye JE, Viel E. Technics of locoregional anesthesia of the lower limb. Phlebologie 1989;42:31-46.
9. Lauretti GR, Hood DD, Eisenach JC, Pfeifer BL. A multi-center study of intrathecal neostigmine for analgesia following vaginal hysterectomy. Anesthesiol 1998;89:913-8.
10. Krukowski JA, Hood DD, Eisenach JC, Mallak KA, Parker RL. Intrathecal neostigmine for post-cesarean section analgesia: dose response. Anesth Analg 1997;84:1269-75.
11. Hood DD, Eisenach JC, Tuttle R. Phase I safety assessment of intrathecal neostigmine methylsulfate in humans. Anesthesiol 1995;82:331-43.
12. Kroin JS, McCarthy RJ, Von Roenn N, Schwab B, Tuman KJ, Ivankovich AD. Magnesium sulfate potentiates morphine antinociception at the spinal level. Anesth Analg 2000;90:913-7.
13. Buvanendran A, McCarthy RJ, Kroin JS, Leong W, Perry P, Tuman KJ. Intrathecal magnesium prolongs fentanyl analgesia: A prospective, randomized, controlled trial. Anesth Analg 2002;95:661-6.
14. Ozalevli M, Cetin TO, Unlugence H, Guler T, Isik G. The effect of adding intrathecal magnesium sulphate to bupivacainefentanyl spinal anaesthesia. Acta Anaesthesiol Scand 2005;49:1514-9.
15. Ghatak T, Chandra G, Malik A, Singh D, Bhatia VK. Evaluation of the effect of magnesium sulphate vs. clonidine as adjunct to epidural bupivacaine. Indian J Anaesth 2010;54:308-13.
16. Taheri R, Shayeghi S, Razavi SS, Sadeghi A, Ghabili K, Ghojazadeh M. Efficacy of bupivacaine-neostigmine and bupivacaine-tramadol in caudal block in pediatric inguinal herniorrhaphy. Paediatr Anaesth 2010;20:866-72.
17. D'Angelo R, Dean LS, Meister GC, Nelson KE. Neostigmine combined with bupivacaine, clonidine, and sufentanil for spinal labor analgesia. Anesth Analg 2001;93:1560-4.
18. Dayioğlu H, Baykara ZN, Salbes A, Solak M, Toker K. Effects of adding magnesium to bupivacaine and fentanyl for spinal anesthesia in knee arthroscopy. J Anesth 2009;23:19-25.
19. Unlugenc H, Ozalevli M, Gunduz M, Gunasti S, Urunsak IF, Guler T, Isik G. Comparison of intrathecal magnesium, fentanyl, or placebo combined with bupivacaine 0.5% for parturients undergoing elective cesarean delivery. Acta Anaesthesiol Scand 2009;53:346-53.
20. Ozalevli M, Cetin TO, Unlugenc H, Guler T, Isik G. The effect of adding intrathecal magnesium sulphate to bupivacaine-fentanyl spinal anaesthesia. Acta Anaesthesiol Scand 2005;49:1514-9.