

Clinical Study

Comparing the Analgesic Efficacy of Intrathecal Bupivacaine Alone with Intrathecal Bupivacaine Midazolam or Magnesium Sulphate Combination in Patients Undergoing Elective Infraumbilical Surgery

Josef Attia, Amany Abo Elhussien, and Mostafa Zaki

Departments of Anesthesiology and ICU, Faculty of Medicine, Minia University, Minia 61111, Egypt

Correspondence should be addressed to Josef Attia; josefzekry2@yahoo.com

Received 14 October 2015; Accepted 28 January 2016

Academic Editor: Bilge Karsli

Copyright © 2016 Josef Attia et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Spinal anaesthesia, which is one of the techniques for infraumbilical surgeries, is most commonly criticized for limited duration of postoperative analgesia. **Aim of the Work.** The aim of this study was to decrease bupivacaine dose used in spinal anesthesia in patients undergoing orthopedic lower limb surgery and reduce its possible side effects. **Patient and Methods.** Sixty adult patients of both sexes, divided into three. **Group C** received 2.5 mL bupivacaine and 0.5 mL saline 0.9%. **Group A** received 2.5 mL bupivacaine and 0.5 mL midazolam. **Group B** received 2.5 mL bupivacaine and 0.5 mL magnesium sulphate. **Results.** As regards onset of both motor and sensory blockade, there are a significant decrease in group A and a significant increase in group B as compared to group C, with a significant decrease in duration of motor blockade and significant increase in duration of sensory blockade in both group A and group B, respectively, as compared to group C, with a significant decrease in the duration of sensory blockade in group B as compared to group C. **Conclusions.** These results suggested that intrathecal midazolam as an adjuvant for bupivacaine increases the duration of both sensory and motor blockade more than that of magnesium sulphate.

1. Introduction

Spinal anesthesia achieved a widespread popularity as a simple and effective method of producing conduction block for surgery in the presence of some ready available drugs, complete aseptic technique, and careful practice; subarachnoid block provides adequate anesthesia for patients undergoing infraumbilical surgery [1].

Among the local anesthetics, 0.5% hyperbaric bupivacaine is the most commonly used drug for spinal anesthesia; however, the most important disadvantage of the single injection is its limited duration [2]. Bupivacaine is a local anesthetic of the amide type, chemically related to mepivacaine; bupivacaine, like other local anesthetics, causes a reversible blockade of impulse propagation along nerve fibers by preventing the inward movement of sodium ions through the nerve membrane. Bupivacaine has a rapid onset and a medium to long duration. The duration is dose-dependent [3].

Midazolam exerts its effect by occupying benzodiazepine receptor that modulates γ -amino butyric acid (GABA), the major inhibitory neurotransmitter in the brain [4, 5]. The hypnotic effects of benzodiazepine are mediated by alterations in the potential dependent calcium ion flux [4]. Midazolam also possesses anticonvulsant action which is attributed to enhanced activity of GABA on motor circuit of brain. It exhibits a muscle relaxant effect via its action as the glycine receptors in the spinal cord [6]. Magnesium has analgesic properties, primarily related to the regulation of calcium influx into cells [7] and antagonism of N-methyl-D-aspartate receptors in the central nervous system [8]. Consequently, it has been suggested that an intrathecal injection would allow more effective magnesium activity at spinal cord NMDA receptors. Indeed, rat models revealed that direct intrathecal administration of magnesium enhances the antinociceptive effect of opioids used in acute incisional pain [9]. The earliest clinical trials investigating intrathecal and epidural magnesium reported an increase in the median duration of analgesia

[10]. The aim of the study is to decrease bupivacaine dose used in spinal anesthesia in patients undergoing orthopedic lower limb surgery and in turn reduce its possible side effects. On the other hand, increase of the time is needed to the first analgesic request; this is achieved by using adjuvant to intrathecal bupivacaine in the form of midazolam or magnesium sulphate.

2. Patients and Methods

After approval of the Local Ethics Committee of Minia University Hospital, informed written consent was obtained from patients. Our study includes 60 patients undergoing orthopedic lower limb surgery in Minia University Hospital.

2.1. Preoperative Assessment. Full medical history and physical examination (chest, heart, abdomen, and other systems) were carried out. Preoperative investigation was done in the form of complete blood count, renal function tests, liver function tests, bleeding time, clotting time, blood sugar, and chest X-ray and ECG if needed. The patient was excluded from the study if the patient is under 18 years old or older than 60, refused to participate, had known hypersensitivity to the drugs and skin infection related to the site of the spinal needle entrance, ASA III or IIIV, had vertebral column deformity, and was pregnant.

2.2. Patients. 60 patients of both sexes are divided into three groups (each group contains 20 patients). *Group C* received 2.5 mL bupivacaine and 0.5 mL saline 0.9%. *Group A* received 2.5 mL bupivacaine and 0.5 mL midazolam (2.5 mg) [11]. *Group B* received 2.5 mL bupivacaine and 0.5 mL magnesium sulphate (50 mg) [11].

2.3. Drug Used. Bupivacaine ampule 4 mL (5 mg in each mL) was purchased from Mylan Company, magnesium sulfate ampule 25 mL (100 mg in each mL) was purchased from Egypt Otsuka Pharmaceutical Co., midazolam ampule 1 mL (5 mg in each mL) was purchased from Roche Company, and saline 0.9% was purchased from Egypt Otsuka Pharmaceutical Co.

2.4. Anesthetic Technique. Patients were taken to the operating room where an intravenous access was assured by inserting an intravenous cannula and all patients received 500 cc lactated Ringer's solution before operation.

After that, patient was prepared to receive spinal anesthesia. An assistant helped maintaining the patient in a comfortable curled position.

Sterilization was done by scrubbing with an antiseptic solution and gloves up carefully and then cleaning the patient's back with the swabs and antiseptic to ensure that gloves do not touch unsterile skin. Swab radially from the proposed injection site and repeat several times making sure that a sufficiently large area was cleaned.

Spinal anesthesia was given at L3/4 interspace using standard spinal anesthesia needle 25 G × 90 mm; the rate of injection was kept 0.2 mL/second. After receiving spinal

TABLE 1: Bromage score.

Score	Definition
0	Able to raise straightened legs against resistance, no detectable motor block.
1	Unable to raise straightened legs, but able to flex knees.
2	Unable to flex knees, but able to flex ankle.
3	Unable to move hip, knee, or ankle.

anesthesia, the patient was put in supine position with head up (30 degrees) and the level of sensory blockade was assessed by pinprick test using visual analogue scale (VAS) and motor blockade was assessed by Bromage scale [11]. Supplemental oxygen was delivered via a nasal cannula just after intrathecal injection.

2.5. Parameters Assessed: The Following Parameters Were Assessed

2.5.1. Level of Sensory Block. Level of sensory block was assessed by VAS using pinprick's test every minute till sensory block occurs at the level of T10 and VAS at this level is zero, and during the postoperative period the test was done every 30 mins till rescue analgesia was needed. VAS score is a tool for assessment of analgesia in the intraoperative and postoperative period. VAS pain score is a linear pain scoring tool ranging from 0 to 100 mm where patients marked a circle around a point (0, 1, 2, 3, etc.) on a 10 cm scale. Duration of analgesia was defined from the administration of subarachnoid block till patient demand for rescue analgesia or VAS value is greater than 40 mm, with one of them earlier than the other [12].

2.5.2. Motor Block. Motor block was assessed by using 4-point Bromage scale. Intraoperative Bromage score was performed every minute after intrathecal injection until achieving Bromage score 3 and then every 30 minutes postoperatively until achieving Bromage score 0 [13] (Table 1).

2.5.3. Hemodynamic Changes. Heart rate, blood pressure, and oxygen saturation were assessed every 10-minute interval till the end of surgery and postoperatively at the following interval (every 30 minutes and then every hour until achieving VAS greater than 4 or Bromage score 3). Only hemodynamic changes that require treatment were considered significant.

2.5.4. Adverse Effects as Sedation. Sedation was assessed according to Ramsay sedation scale [14].

3. Statistical Analysis of the Data

Data were checked, coded, entered, and analyzed by using SPSS (the Statistical Package for Social Sciences) version 17.0 software [8]. Recorded values were presented as means ± standard deviation. Statistical analysis included parametric and nonparametric methods by one-way or two-way analysis

TABLE 2: Onset of motor blockade and duration of motor blockade.

Groups	Onset of motor blockade (min)	Duration of motor blockade (min)
Group C	4.7 ± 0.44	263 ± 48
Group A	3.1 ± 1.3 ^a	162 ± 27.3 ^a
Group B	6 ± 2.8 ^{ab}	126 ± 33 ^{ab}

Data represented as mean ± SD, P value < 0.05. ^aSignificant changes from group C and ^bsignificant changes from group A.

of variance (ANOVA) among the 3 different groups. Categorical data were compared using the Fisher exact test. A value of $P < 0.05$ was considered statistically significant.

4. Results

4.1. Demographic Data (Patient Characteristics). There were no statistically significant differences ($P < 0.05$) between three groups as regards age, mean body mass index (Table 2).

4.2. Onset and Duration of Motor Blockade. As regards the onset of motor blockade, there was a significant decrease in onset of motor blockade in group A (3.1 ± 1.3 min) as compared to group C (4.7 ± 0.44 min). However, a significant increase was detected in group B (6 ± 2.8 min) as compared to group C (4.7 ± 0.44 min) and group A (3.1 ± 1.3 min).

On the other hand, there was a significant decrease in duration of motor blockade in both group A and group B, respectively (162 ± 27.3 and 126 ± 33 min), as compared to group C (263 ± 48 min) with a significant decrease in the duration of motor blockade group B (126 ± 33 min) as compared to group C (263 ± 48 min) (Table 1).

4.3. Onset and Duration of Sensory Blockade. As regards the onset of sensory blockade, there was a significant decrease in onset of sensory blockade in group A (3.7 ± 1.13 min) as compared to group C (5 ± 1.1 min). However, a significant increase was detected in group B (6.6 ± 2.7 min) as compared to group C (5 ± 1.1 min) and group A (3.7 ± 1.13 min).

On the other hand, there was a significant increase in duration of sensory blockade in both group A and group B, respectively (253 ± 53 and 157 ± 36 min), as compared to group C (112 ± 15 min) with a significant decrease in the duration of sensory blockade group B (157 ± 36 min) as compared to group C (112 ± 15 min) (Table 3).

4.4. Hemodynamic Changes. There were no significant changes in mean arterial blood pressure (mmHg) at any time during the study periods (preoperatively, intraoperatively, and postoperatively) inside each group or between the three groups (Figure 1).

4.5. Adverse Effects as Sedation. We did not detect any degree of sedation in the three groups of our study.

4.5.1. Heart Rate. There were no significant changes in heart rate (beat/min) at any time during the study periods

TABLE 3: Onset of sensory blockade and duration of sensory blockade.

Groups	Onset of sensory blockade (min)	Duration of sensory blockade (min)
Group C	5 ± 1.1	112 ± 15
Group A	3.7 ± 1.13 ^a	253 ± 53 ^a
Group B	6.6 ± 2.7 ^{ab}	157 ± 36 ^{ab}

Data represented as mean ± SD, P value < 0.05. ^aSignificant changes from group C and ^bsignificant changes from group A.

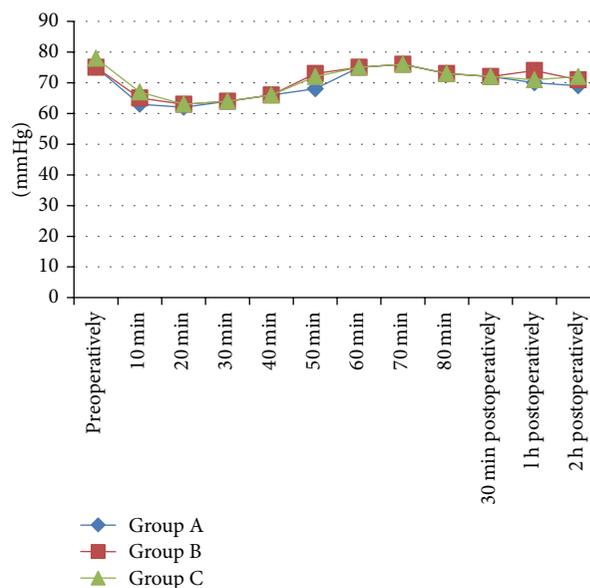


FIGURE 1: Mean arterial blood pressure changes in the study group.

(preoperatively, intraoperatively, and postoperatively) inside each group or between the three groups (Figure 2).

5. Discussion

The onset and duration of spinal anesthesia have greater concern in anesthetic practices, so many studies used midazolam as an adjuvant to bupivacaine in spinal anesthesia [15–17]. Also many studies used magnesium sulphate as an adjuvant [18–20].

As regards the duration of sensory blockade there was a significant prolongation of sensory blockade (the duration from the sensory block after spinal procedure determined by VAS reaching zero value till patient demand for rescue analgesia or VAS value is greater than 40 mm, with one of them earlier than the other); it was significantly higher in patients receiving midazolam as an adjuvant more than the other two groups. This is due to the benzodiazepine receptors which present in the spinal cord and in turn trigger the use of intrathecal midazolam for prolongation of spinal anesthesia [21]. In vitro autoradiography has shown that there is a high density of benzodiazepine receptors in Lamina II of the dorsal horn in the human spinal cord suggesting a possible role in pain modulation [11].

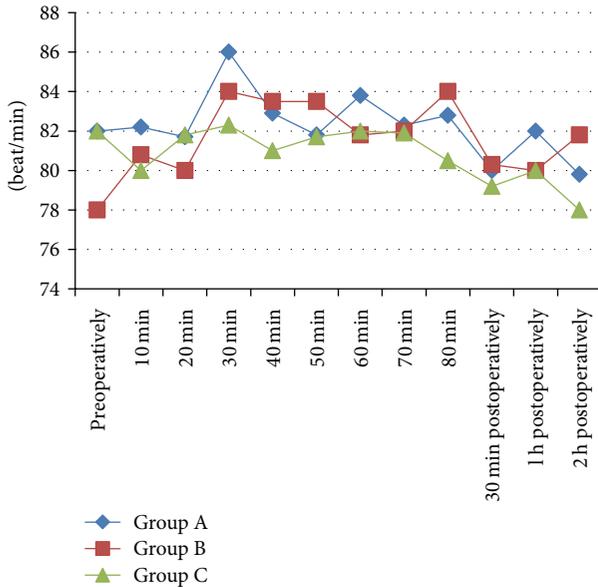


FIGURE 2: Mean of heart rate changes in the study group.

Batra et al. [22] reported a similar finding in which intrathecal administration of midazolam along with bupivacaine produces better postoperative analgesia and a prolonged sensory blockade. Furthermore, Kim and Lee [15] reported that, in a meta-analysis, addition of 1 or 2 mg of intrathecal midazolam prolonged the postoperative analgesic effect of bupivacaine by approximately 2 h and 4.5 h, respectively, as compared to control group after hemorrhoidectomy, and this finding suggested a dose-dependent action of intrathecal midazolam. It was reported that hemorrhoidectomy pain can be alleviated only by sacral sensory nerves. Our patients were undergoing lower limb surgeries, and, for effective analgesia, these patients require blockade of lower lumbar dermatomes as well. Furthermore, we found that intrathecal midazolam at a dose of 2.5 mg significantly prolonged the duration of motor block and in turn must be put into consideration when early ambulation is desirable. Bharti et al. [23] reported a prolonged sensory and motor block following midazolam administration as adjuvant with bupivacaine in lower abdominal surgery occurred.

Our study showed prolongation of motor and sensory blockade in magnesium sulphate-treated group as compared with control group although it is less than that in intrathecal group. These midazolam-treated results are consistent with a previous study conducted by Arcioni et al. [18]. In studies done by Lee et al. [19] in which 50 mg magnesium sulfate was given intrathecally to patients undergoing total knee replacement, knee arthroscopy, and thoracic surgery they observed that the VRS scores at first analgesic requirement and 36 h morphine requirement were significantly lower after intrathecal injection of magnesium sulfate, respectively, as compared with the control group. Nath et al. [24] reported a delay in sensory recovery and motor blockade after intrathecal magnesium sulphate and this result is in contrast to our result with different dose.

Our result was in contrast to that of Unlugenc and colleagues [25] who reported that in a study done on ninety patients undergoing cesarean section there was a decrease in the duration of analgesia with the addition of intrathecal magnesium sulphate and this may be due to the small dose of intrathecal bupivacaine (10 mg) used and different surgical procedure (caesarean section) as compared with our study, where we used 12.5 mg of heavy bupivacaine for lower limb surgery, although their results showed a delay in the onset of sensory and motor blockade as what we had found in our study results. Dayioğlu et al. [26] also did not report any increase in the duration of the motor blockade in a study done on 60 patients.

As regards the motor and sensory onset, our study results showed a significant delay in the onset of both sensory and motor blockade with the intrathecal magnesium sulphate. Özalevli et al. [27] observed a similar delay in onset of spinal anesthesia when they added intrathecal magnesium sulphate to fentanyl and isobaric bupivacaine. In addition, Malleeswaran et al. [28] reported a delay in sensory and motor onset in a study conducted on sixty women with mild preeclampsia undergoing caesarean section.

As regards the complications and adverse effects, we found that both of magnesium sulphate and midazolam did not cause any obvious side effect as hypotension, bradycardia. In previous studies midazolam has been administered in the dose of 1 mg, 2 mg, and 2.5 mg intrathecally [16, 29].

The safety of intrathecal magnesium administration has been evaluated in animal and human studies. Lee et al. [19] evaluated the safety profile of magnesium sulphate in several experimental settings, including histopathological analysis; thus intrathecal magnesium seems to have a good safety profile. This is comparable to our study where there were no side effects related to the drug.

Hemodynamic changes were assessed by frequent monitoring and recording of heart rate and blood pressure preoperatively, intraoperatively, and postoperatively and we found that there were no significant differences between the study groups. The results of our study were comparable with those of Agrawal et al. [29] and Kim and Lee [15]. Aikta et al. [16] reported that there were no significant hemodynamic changes in studies that used magnesium sulfate as an adjuvant to bupivacaine in spinal anesthesia.

As regards the sedation we did not detect any degree of sedation in the three groups of our study, and this result was consistent with that of Chattopadhyay et al. [17] who reported a prolongation of the sensory blockade without any side effects when using intrathecal midazolam 2 mg with 0.5 bupivacaine.

However, it is in contrast to Yegin et al. [30] who reported a prolonged analgesia with mild sedation in perianal cases on using a higher dose midazolam (5 mg) and that is maybe the cause of the sedation in their study.

As far as we could know sedation with the use of magnesium sulphate intrathecally was not detectable in any study done on intrathecal magnesium administration [28]. This result is the same as what we had found in our study, as we did not detect any level of sedation with the magnesium sulphate group.

6. Conclusion

Both of midazolam and magnesium sulphate increase the duration of both sensory and motor blockade of spinal anesthesia when being used as an adjuvant for bupivacaine, with less side effects. Intrathecal midazolam 2.5 mg as an adjuvant for bupivacaine increases the duration of both sensory and motor blockade more than that of magnesium sulphate.

7. Recommendations

Our study was limited to lower limb surgeries, so we recommend further studies on different types of operations as caesarian sections, hysterectomy, and abdominal surgeries; another recommendation is to compare midazolam and the other adjuvants as opioids with the use of the different approved doses of intrathecal midazolam.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

Authors' Contributions

All authors contributed equally to the paper.

References

- [1] M. J. Cousins, P. O. Bridenbaugh, D. B. Carr, and T. T. Horlocker, *Neural Blockade in Clinical Anesthesia and Pain Medicine*, chapter 1, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 4th edition, 2008.
- [2] J. Morgan, M. Mikhail, M. Murray, and J. Larson, *Clinical Anaesthesiology*, Lange, New York, NY, USA, 4th edition, 2002.
- [3] B. Cox, M. E. Durieux, and M. A. E. Marcus, "Toxicity of local anaesthetics," *Best Practice and Research: Clinical Anaesthesiology*, vol. 17, no. 1, pp. 111–136, 2003.
- [4] W. B. Mendelson, "Neuropharmacology of sleep induction by benzodiazepines," *Critical Reviews in Neurobiology*, vol. 6, no. 4, pp. 221–232, 1992.
- [5] P. G. Strange, "D1/D2 dopamine receptor interaction at the biochemical level," *Trends in Pharmacological Sciences*, vol. 12, pp. 48–49, 1991.
- [6] J. G. Reves, R. J. Fragen, H. R. Vinik, and D. J. Greenblatt, "Midazolam: pharmacology and uses," *Anesthesiology*, vol. 62, no. 3, pp. 310–324, 1985.
- [7] L. T. Iseri and J. H. French, "Magnesium: nature's physiologic calcium blocker," *American Heart Journal*, vol. 108, no. 1, pp. 188–193, 1984.
- [8] C. J. Woolf and S. W. N. Thompson, "The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states," *Pain*, vol. 44, no. 3, pp. 293–299, 1991.
- [9] J. S. Kroin, R. J. McCarthy, N. Von Roenn, B. Schwab, K. J. Tuman, and A. D. Ivankovich, "Magnesium sulfate potentiates morphine antinociception at the spinal level," *Anesthesia & Analgesia*, vol. 9, no. 4, pp. 913–917, 2000.
- [10] A. Buvanendran, R. J. McCarthy, J. S. Kroin, W. Leong, P. Perry, and K. J. Tuman, "Intrathecal magnesium prolongs fentanyl analgesia: a prospective, randomized, controlled trial," *Anesthesia and Analgesia*, vol. 95, no. 3, pp. 661–666, 2002.
- [11] R. L. M. Faull and J. W. Villiger, "Benzodiazepine receptors in the human spinal cord: a detailed anatomical and pharmacological study," *Neuroscience*, vol. 17, no. 3, pp. 791–802, 1986.
- [12] M. E. Wewers and N. K. Lowe, "A critical review of visual analogue scales in the measurement of clinical phenomena," *Research In Nursing & Health*, vol. 13, no. 4, pp. 227–236, 1990.
- [13] P. R. Bromage, "Neurological complications of epidural and spinal techniques," *Baillière's Clinical Anaesthesiology*, vol. 7, no. 3, pp. 793–815, 1993.
- [14] H. Reschreiter and A. Kapila, "Sedation in adults," *Surgery (Oxford)*, vol. 24, no. 10, pp. 342–345, 2006.
- [15] M. H. Kim and Y. M. Lee, "Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy," *British Journal of Anaesthesia*, vol. 86, no. 1, pp. 77–79, 2001.
- [16] G. Aikta, P. Smita, D. Savita, and K. Kake, "The effect of intrathecal midazolam 2.5 mg with bupivacaine on postoperative pain relief in patients undergoing orthopaedic surgery," *Journal of Anaesthesiology Clinical Pharmacology*, vol. 24, no. 2, pp. 189–192, 2008.
- [17] A. Chattopadhyay, S. Maitra, S. Sen et al., "A study to compare the analgesic efficacy of intrathecal bupivacaine alone with intrathecal bupivacaine midazolam combination in patients undergoing elective infraumbilical surgery," *Anesthesiology Research and Practice*, vol. 2013, Article ID 567134, 5 pages, 2013.
- [18] R. Arcioni, S. Palmisani, C. Santorsola et al., "Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce post-operative analgesic requirements: a prospective, randomized, double-blind, controlled trial in patients undergoing major orthopedic surgery," *Acta Anaesthesiologica Scandinavica*, vol. 51, no. 4, pp. 482–489, 2007.
- [19] J. W. Lee, M. K. Kim, Y. Shin, and B. Koo, "The analgesic effect of single dose of intrathecal magnesium sulfate," *Korean Journal of Anesthesiology*, vol. 52, no. 6, pp. S72–S76, 2007.
- [20] S. Paul, D. P. Bhattacharjee, S. Ghosh, and N. Chatterjee, "Efficacy and safety of intrathecal magnesium sulphate as an adjuvant to bupivacaine for lower limb orthopedic surgery," *Pharmacologyonline*, vol. 2, pp. 570–574, 2009.
- [21] H. Mohler and T. Okada, "Benzodiazepine receptor: demonstration in the central nervous system," *Science*, vol. 198, no. 4319, pp. 849–851, 1977.
- [22] Y. K. Batra, K. Jain, P. Chari, M. S. Dhillon, B. Shaheen, and G. M. Reddy, "Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery," *International Journal of Clinical Pharmacology and Therapeutics*, vol. 37, no. 10, pp. 519–523, 1999.
- [23] N. Bharti, R. Madan, P. R. Mohanty, and H. L. kaul, "Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia," *Acta Anaesthesiologica Scandinavica*, vol. 47, no. 9, pp. 1101–1105, 2003.
- [24] M. P. Nath, A. Chakrabarty, D. Choudhary, R. Garg, and T. Talukdar, "To evaluate the efficacy of intrathecal magnesium sulphate for hysterectomy under subarachnoid block with bupivacaine and fentanyl: a prospective randomized double blind clinical trial," *Saudi Journal of Anaesthesia*, vol. 6, no. 3, pp. 254–258, 2012.
- [25] H. Unlugenc, M. Ozalevli, M. Gunduz et al., "Comparison of intrathecal magnesium, fentanyl, or placebo combined with

- bupivacaine 0.5% for parturients undergoing elective cesarean delivery," *Acta Anaesthesiologica Scandinavica*, vol. 53, no. 3, pp. 346–353, 2009.
- [26] H. Dayioğlu, Z. N. Baykara, A. Salbes, M. Solak, and K. Toker, "Effects of adding magnesium to bupivacaine and fentanyl for spinal anesthesia in knee arthroscopy," *Journal of Anesthesia*, vol. 23, no. 1, pp. 19–25, 2009.
- [27] M. Özalevli, T. O. Cetin, H. Unlugenc, T. Guler, and G. Isik, "The effect of adding intrathecal magnesium sulphate to bupivacaine-fentanyl spinal anaesthesia," *Acta Anaesthesiologica Scandinavica*, vol. 49, no. 10, pp. 1514–1519, 2005.
- [28] S. Malleeswaran, N. Panda, P. Mathew, and R. Bagga, "A randomised study of magnesium sulphate as an adjuvant to intrathecal bupivacaine in patients with mild preeclampsia undergoing caesarean section," *International Journal of Obstetric Anesthesia*, vol. 19, no. 2, pp. 161–166, 2010.
- [29] N. Agrawal, A. Usmani, R. Sehgal, R. Kumar, and P. Bhadoria, "Effect of intrathecal midazolam bupivacaine combination on post operative analgesia," *Indian Journal of Anaesthesia*, vol. 49, no. 1, pp. 37–39, 2005.
- [30] A. Yegin, S. Sanli, L. Dosemeci, N. Kayacan, M. Akbas, and B. Karsli, "The analgesic and sedative effects of intrathecal midazolam in perianal surgery," *European Journal of Anaesthesiology*, vol. 21, no. 8, pp. 658–662, 2004.



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

