Available online at www.jsan.org.np

Journal of Society of Anesthesiologists of Nepal

Original Article

Intrathecal Magnesium Sulfate as Analgesic and Anaesthetic Adjunct to Bupivacaine in Patients Undergoing Lower Extremity Orthopaedic Surgery

Prakash Maden Limbu[1], Sindhu Khatiwada[1], Birendra Prasad Sah[1], Satyendra Narayan Singh[1], Krishna Pokharel[1], Rajiv Maharjan[2]

1 Department of Anaesthesiolgy & Critical Care Medicine, B.P. Koirala Institute of Health Sciences, Buddha Road, Dharan, 56700

2 Department of Orthopaedics, B.P. Koirala Institute of Health Sciences, Buddha Road, Dharan, 56700

Corresponding Author
Dr Prakash Maden Limbu, MD
Department of Anaesthesiology and Critical Care Medicine,
B.P. Koirala Institute of Health Sciences, Buddha Road,
Dharan 56700, Nepal
Email: kashlimbu@hotmail.com

Abstract

Background

Subarachnoid block is a popular mode of anesthesia for lower limb surgeries. Studies of Magnesium Sulfate ($MgS0_4$) as an adjuvant to intrathecal local anaesthetic are limited. The objective was to find out the analgesic and anaesthetic effect of intrathecal $MgS0_4$ added to bupivacaine for spinal anaesthesia in patients undergoing lower extremity orthopaedic surgery.

Methods

Sixty ASA I or II adult patients undergoing lower extremity orthopaedic surgery were randomly allocated in a double blinded fashion into two groups of thirty each. Group A received 3.0 ml of 0.5% hyperbaric bupivacaine with 0.15 ml of 50% $MgSO_4$. Group B received 3.0 ml of 0.5% hyperbaric bupivacaine with 0.15 ml of NS. Onset of sensory and motor block as well as time to attain highest level of sensory block were recorded. Duration of sensory and motor block along with duration of spinal anaesthesia were also assessed. Any adverse effects were noted and treated.

Results

Duration of sensory and motor block along with duration of spinal anaesthesia were prolonged in patients of $MgSO_4$ but were not statistically significant with p-value of 0.33, 0.23 and 0.68 respectively. Onset of anaesthesia, requirement of rescue analgesics, haemodynamic parameters and adverse effects were comparable between two groups.

Conclusion

In patients undergoing lower extremity orthopaedic surgery the addition of 75mg of $MgSO_4$ to intrathecal bupivacaine did not prolong the duration of sensory block, spinal anaesthesia nor decreased postoperative analgesic consumption without any additional side effects.

Keywords: Bupivacaine, Intrathecal Magnesium Sulfate, Spinal Anaesthesia

Article History
Received 18th December 2017
Accepted 3rd March 2018
Published 17th August 2018

How to cite this article: Limbu PM, Sindhu K, Singh SN, Pokharel K, Maharjan R. Intrathecal Magnesium Sulfate as Analgesic and Anaesthetic Adjunct to Bupivacaine in Patients Undergoing Lower Extremity Orthopaedic Surgery. Journal of Society of Anesthesiologists of Nepal (JSAN) 2017;4(2):74-80

Introduction

Pain has adverse physiologic effects that can contribute to significant morbidity and mortality.[1] Adequate post-operative analgesia is very important as it is associated with less physiological derangement with quicker recovery and ambulation.

Subarachnoid block (SAB) is a popular mode of anaesthesia for lower limb surgeries. It reduces perioperative complications and provides superior analgesia compared to general anaesthesia.[2] Various intrathecal adjuvants are in use with local anaesthetics (LA) to provide intraoperative and prolonged post-operative analgesia. Agents like opioids,[3] clonidine,[4] dexmedetomidine,[5] neostigmine,[6] midazolam[7] and dexamethasone[8] have been used with varying result as an adjuvant to LA but with various side effects. [3,9–13]

Recently Magnesium Sulfate ($MgSO_4$) has gained popularity as an adjuvant to LA or spinal anesthesia. Studies on the use of intrathecal $MgSO_4$ added only to LA for spinal anaesthesia are very few in number.[14,15] There is no evidence that $MgSO_4$ is harmful to spinal tissue and severe side effects with low dose intrathecal $MgSO_4$ has not been seen.[14,16–20] Even with an inadvertent intrathecal injection of 1500 mg for emergency strangulated inguinal hernia repair patient recovered back to normal on fifth day without any residual complicatons in a report by Najafi et al.[21]At present there is still in need of an ideal intrathecal adjuvant which would prolong the duration of anaesthesia and analgesia. Perhaps $MgSO_4$ could be the one that we are looking for. This study was therefore conducted to find out the analgesic and anesthetic effect of intrathecal $MgSO_4$ added to LA for SAB in patients undergoing lower extremity orthopaedic surgery.

Methods

This was a prospective randomized double blind controlled clinical trial conducted from July 2014 to July 2015 in the department of Anaesthesiology & Critical Care at B.P. Koirala Institute of Health Sciences, Dharan with approval from the Institutional Review Committee (IRC). Informed written consent from the patient was taken. Sixty patients of either gender aged 18-65 years with American Society of Anesthesiologists physical status (ASA PS) I and II scheduled for SAB for various lower extremity orthopaedic surgery were included and randomly divided into two groups of 30 each in $MgSO_4$ and NS. Randomization was based on computer generated random number table. A total of 60 concealed envelopes were made mentioning the study group inside and the sequence number on the outside along with the study solution to be given for SAB. Drug preparation was made by an anaesthesiologist not involved in the study. The participants & the investigator involved in collecting data and in the assessment of outcome variable were unaware regarding group allocation. Groups were disclosed only during data analysis.

Patients refusing to participate in the study, ASA PS ≥ III, any contraindication for SAB, height < 5 ft., allergy to study drugs, requiring general anaethesia for any reason were excluded.

Sample size estimation was based on duration of sensory block on a study done by Khalili Gholamreza et al.[14] Duration of sensory block in their study in each group was normally distributed with standard deviation of 22 min and 15.3 min in $MgSO_4$ and NS group respectively. Difference in two mean duration between the groups was at least 21. So sample size taken was 30 in each group which was enough to reject null hypothesis with probability of power 95% & 5% level of significance.

One day prior surgery, each patient and their relatives were explained about the study. The patients were instructed about the assessment of pain in the postoperative period by visual analog scale (VAS) (0 no pain at all and 10 maximum pain attainable). All patients were kept NPO for eight hours and received diazepam 0.2 mg/kg not exceeding 10 mg as pre medication in the evening a day before surgery and in morning two hours before surgery. After arrival of the patient to the operating room electrocardiogram (ECG), noninvasive blood pressure (NIBP) and pulse oximeter were attached to the patient and baseline measurements of heart rate (HR) , blood pressure(BP), peripheral oxygen saturation (SpO_2) and respiratory rate(RR) were recorded. These were recorded five minutes before intrathecal injection and every ten minutes until the completion of surgery. Patients were preloaded with 500ml of Ringers' lactate (RL) over a period of 20 min prior to SAB. Patient in $MgSo_4$ group received 3.0 ml of 0.5% hyperbaric bupivacaine (15 mg) with 0.15 ml of 50% $MgSO_4$ (75 mg). Patient in NS group received 3.0 ml of 0.5% hyperbaric bupivacaine (15 mg) with 0.15 ml NS. Both groups received a total volume 3.15 ml & since both NS & $MgSO_4$ were colourless & similar looking blinding was maintained. Subarachnoid block was done with 25 Gauge Quincke's needle at L3-4 or L4-L5 interspace.

Anaesthetic features of SAB were defined and evaluated as follows after SAB .[14] Onset of sensory blockade was defined as time taken to achieve loss of pinprick sensation to 23 G hypodermic needle tested every two minute at T10 dermatome. Time of highest dermatome level of sensory blockade was defined as

the time taken for loss of pinprick sensation to 23 G hypodermic needle tested every two minutes until highest level had stabilized for four consecutive tests. Duration of sensory block was defined as time taken to regress from the highest level of loss of pinprick sensation achieved to two lower sensory dermatome level tested every 10 min after 60 min of SAB. Duration of spinal anaesthsia was defined as time taken from the time of spinal injection to the time when the patient complained of pain at surgical site or VAS > three. Motor block was assessed based on Modified Bromage Scale.[22] Onset of motor block was defined as time taken to reach a bromage scale of two tested every two minutes. Duration of motor block was defined as duration from time of injection till the patient attained complete motor recovery of lower limb *i.e.* Bromage scale of 0.

Adverse events were observed in the intraoperative as well as in the post anaesthetic care unit (PACU). Hypotension was defined as a decrease in systolic blood pressure (SBP) by > 20% from baseline or < 90 mm Hg. Inj. Phenylephreine 50 μcg IV stat. was given as intervention. Bradycardia was defined as HR < 50 bpm. Atropine 0.3 mg IV stat was given as intervention. Nausea and vomiting was rated on a scale of 0 to three.[23] It was treated by ondansetron 4 mg intravenously. Shivering was graded using a scale by Tsai and Chu.[24] Shivering score of one to two was treated by infusing warm IV fluids. Score of three and four was treated with ondansetron 4 mg intravenously.

Pain was evaluated using VAS score in the postoperative period at every 15 min for the first hour and every 20 min in the next hour. Diclofenac 75 mg IM was given 1 hour after SAB. Second dose of diclofenac was given when patient first complained of pain and was repeated every eight hourly for 24 h. If the VAS > three or patient complained of pain at least 15 min after diclofenac administration, tramadol 100 mg IV as a rescue analgesic was administered. If the patient still complained of persistent pain or had VAS > 3 despite giving tramadol, Morphine 0.05 mg/kg IV was added as a second rescue analgesic. Morphine was added only after 10 min of tramadol administration. The number of rescue analgesics required in first 24 h were noted.

Our primary outcome measure was duration of sensory block . Other anaesthetic parameters including onset of sensory & motor block, duration of spinal anaesthesia & motor block, time to attain highest level of sensory block and postoperative analgesic consumption were secondary outcome measures.

Statistical analysis was done accordingly. Normally distributed interval data such as demographic variables like age, height, Ideal body weight (IBW) and preoperative haemodynamics HR, BP, RR and SpO_2 were analyzed using unpaired t-test.. Categorical values such as gender and ASA PS were analyzed using Pearson chi-square Test. Anaesthetic effects in terms of time in minutes such as onset of sensory, motor & time to attain highest level of sensory block were analyzed using Mann Whitney U test since the data were in non normal distribution. Other anaesthetic parameters in normal distribution such as duration of sensory, motor block and spinal anaesthesia were analyzed using unpaired t-test. For all the tests p value <0.05 was considered statistically significant.

Results

Sixty recruited patients randomly grouped into two were compared with regards to demographic and hemodynamics characteristics, VAS for pain, requirement of rescue analgesic and anaesthetic effects. Demographic variables age, height, IBW, gender and ASA in both groups were similar (Table 1).

Table 1: Characteristics of patients between two groups

Parameters	Group A (MgSO4) (n=30)	Group B (NS) (n=30)	P - Value
Age (years)	44.67 ± 15.64	38.03 ± 16.39	0.88
Height (cm)	165.10 ± 6.26	166.03 ± 5.48	0.60
Ideal Body Weight (kg)	60.63 ± 7.12	61.77 ± 5.84	0.21
Gender M:F (n)	21:9	23:7	0.56
ASA I:II (n)	22:8	27:3	0.095

Data are presented as the mean ± Standard Deviation except for Gender & ASA for which data are presented as number (n)

Preoperative haemodynamics parameters HR, SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), RR & SpO_2 in both groups were comparable (Table 2).

Table 2: Comparison of preoperative haemodynamics between two groups.

Characteristics	Group A ($MgSO_4$) (n=30)	Group B (NS) (n=30)	P-value
Heart Rate (per min)	86.47 ± 14.77	87.77 ± 17.06	0.57
Systolic Blood Pressure (mmHg)	122.73 ± 15.20	129.10 ± 16.39	0.95

Diastolic Blood Pressure (mmHg)	74.70 ± 10.13	78.27 ± 10.79	0.87
Mean Arterial Pressure (mmHg)	91.03 ± 10.91	95.50 ± 11.24	0.87
Respiratory Rate (per min)	15.30 ± 2.62	15.33 ± 2.01	0.09
SpO_2 (%)	99.40 ± 0.86	99.47 ± 0.90	0.94

n=number

Data are presented as the mean ± Standard Deviation

Intraoperative haemodynamics measured every 10 min after SAB till the end of surgery were also similar between two groups at different time intervals.

Anaesthetic effects were compared between the two groups (Table 3) .

Table 3: Comparison of anaesthetic effect between two groups

Parameters (Minutes)	Group A (MgSO4) (n=30)	Group B (NS) (n=30)	P-value
Onset of sensory block	3.43 ± 1.41	3.97 ± 1.59	0.18 *
Time to attain highest level of sensory block	8.50 ± 4.67	10.90 ± 5.20	0.08 *
Onset of motor block	4.53 ± 2.33	4.4 ± 1.77	0.80 *
Duration of sensory block	92.33 ± 13.57	88.67 ± 15.48	0.33
Duration of spinal anaesthesia	292.00 ± 106.93	282.17 ± 72.03	0.68
Duration of motor block	222.33 ± 59.77	204.13 ± 56.89	0.23

*indicates Mann Whitney U test ;n=number, Data are presented as the mean ± Standard Deviation

Onset of sensory and motor block as well as time to attain highest level of sensory block were similar. Duration of sensory & motor block along with duration of spinal anaesthesia were prolonged in patients of magnesium group but were not statistically significant.

Visual Analog Score was compared between two groups over two hours after surgery, which was tested every 15 min for 1st hour then every 20 min for 2nd hour. It was similar over the duration of 2 hours. A total of 5 (17%) patients in $MgSO_4$ group required rescue analgesic in comparison to 6 (20%) patients in NS group during 1st 24 h after SAB. Number of rescue analgesic required in NS was more but was not statistically significant (p=0.74).

Adverse events observed were mild in severity as in table 4.

Table 4: **Comparison of adverse effects between two groups**

	Group A ($MgSO_4$ (n=30)	Group (NS) (n=30)	P-value
Hypotension	7	5	0.52
Bradycardia	3	3	1
Shivering	1	1	1

n=number

Data are presented as no. of patients.

There were no significant differences between the two groups.

Discussion

Intrathecal $MgSO_4$ when combined with opioid and LA agent is known to potentiate the analgesic effect of an opioid.[6,17,18,25] Inhibition of calcium influx is presumed to augment opioid-induced analgesia. Potentiation of the analgesic effect of LA agent with intrathecal $MgSO_4$ has also been suggested. The addition of magnesium reduces the activation of c-fibres by inhibiting the slow excitatory postoperative-synaptic currents produced by NMDA receptor activation.[26] Magnesium acting as NMDA receptor antagonist abolish calcium and sodium influx into cells leading to central sensitization and wind up attributed to peripheral nociceptive stimulation.[27,28] They abolish hypersensitization by blocking NMDA receptor activation in the dorsal horn by excitatory amino acid transmitters, notably glutamate and aspartate.[28]

Various doses of intrathecal magnesium sulfate have been used ranging from 50mg to 100 mg with 50 mg being the most commonly used dose. However 50 mg of intrathecal $MgSO_4$ when combined with bupivacaine alone did not prolong spinal anaesthesia in a study done by Jabalameli et al.[15] We chose 75 mg as this dose was enough to prolong the duration of sensory and motor blockade without increasing the frequency of major adverse effects in comparison to 100 mg in the same study.

The anaesthetic effect was compared between two groups. The onset of sensory, motor block and time to attain highest dermatome level of sensory block were comparable in both groups. Our results were similar to Faiz et al.[6] where intrathecal $MgSO_4$ had no effect on the

onset of sensory or motor block but contrasted to other studies.[5,7,14] The authors of these studies suggested that differences in the pH and baricity of the solution containing $MgSO_4$ could have contributed to the delayed onset. Similarly intrathecal $MgSO_4$ did not prolong the duration of sensory or motor blockade as compared to NS in our study. Our findings is similar to study by Khalili et al.[14] but in contrary to Ulgenc et al.[25] Intrathecal fentanyl in combination with $MgSO_4$ and bupivacaine could have played a role. Duration of spinal anaesthesia was prolonged by almost 10 min in the $MgSO_4$ group but was not long enough to reach statistical significance similar to a report by Khalili et al.[14] Our finding suggest that 75mg of intrathecal $MgSO_4$ added to hyperbaric bupivacaine does not prolong the duration of spinal anaesthesia. On the other hand use of diclofenac one hour after SAB in our study could have masked the pain in the immediate postoperative period.

Visual Analog Score was comparable in both the groups. The requirement of tramadol and morphine as rescue analgesics was comparable in both groups over 24 hours similar to the findings of Dayioglu et al.[25] and Buvanendran et al.[16] Use of lower dose (75 mg) of $MgSO_4$ could be the reason for not decreasing the requirement of rescue analgesic in our patients. In contrast Khalili et al.[14] observed the opioid sparing effect of intrathecal $MgSO_4$ when used in a higher dose of 100 mg. Lesser requirement of analgesic was also reported by Malleeswaran et al.[17] Fentanyl in addition to intrathecal $MgSO_4$ could have played a role producing opioid sparing effect leading to decrease in analgesic consumption.

Occurrence of hypotension, bradycardia and shivering were common adverse effects which were comparable between the two groups similar to a study by Unlugenc et al.[19] These events may be merely due to the effect of SAB related to bupivacaine.

There are several limitation to the study . Our study involved all types of procedure on different locations of lower limb including femur, tibia or fibula. Perhaps study involving a specific location would have better results in terms of postoperative analgesic consumption. Study with a larger dose of intrathecal magnesium or a larger sample size might have shown significant difference in analgesic and anaesthetic effect.

Conclusion

In patients undergoing lower extremity orthopaedic surgery the addition of 75mg of $MgSO_4$ to intrathecal bupivacaine did not prolong the duration of sensory block, spinal anaesthesia nor decreased postoperative analgesic consumption without any additional side effects.

Acknowledgement: Dr. Ashish Ghimire
Conflict of interest: All authors have filled the ICMJE conflict of interest form and declare that they have nothing to disclose.
Sources of funding: None

References

1. Wu C, Naqibuddin M, Rowlingson A, Lietman S, Jermyn R, Fleisher L. The effect of pain on health-related quality of life in the immediate postoperative period. Anesth Analg. 2003;97(4):1078–85. https://doi.org/10.1213/01.ANE.0000081722.09164.D5 PMid:14500161

2. Urban M. Anaesthesia for orthopaedic surgery. In: Cohen NH, Eriksoson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's Anaesthesia. 8th ed. 2015. p. 2386–406.

3. Hurley R, Murphy J, Wu C. Acute postoperative pain. In: Cohen NH, Eriksoson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's Anaesthesia. 8th ed. Elsevier Ltd; 2015. p. 2974–96.

4. Singh R, Gupta D, Jain A. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section: A randomized control trial. Saudi J Anaesth. 2013 Jul;7(3):283–90. https://doi.org/10.4103/1658-354X.115360 PMid:24015131 PMCid:PMC3757801

5. Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C. Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine. J Anaesthesiol Clin Pharmacol. 2011 Oct;27(4):495–9. https://doi.org/10.4103/0970-9185.86594 PMid:22096283 PMCid:PMC3214555

6. Faiz SHR, Rahimzadeh P, Sakhaei M, Imani F, Derakhshan P. Anesthetic effects of adding intrathecal neostigmine or magnesium sulphate to bupivacaine in patients under lower extremities

surgeries. J Res Med Sci. 2012 Oct;17(10):918–22. PMid:23825989 PMCid:PMC3698648

7. Shashni S, Nair AS, Gopal TVS. Clinical effects of intrathecal midazolam versus intrathecal magnesium sulfate as adjuncts to hyperbaric bupivacaine: A comparative study. Indian J Pain. 2013;27(3):175. https://doi.org/10.4103/0970-5333.124604

8. Jabbari A, Hassan-nasab B, Maleh P, Bani-hashem N, Pour E, Nabavi A. Addition of intrathecal Dexamethasone to Bupivacaine for spinal anesthesia in orthopedic surgery. Vol. 5, Saudi Journal of Anaesthesia. 2011. p. 382. https://doi.org/10.4103/1658-354X.87267 PMid:22144925 PMCid:PMC3227307

9. Niu X-Y, Ding X-B, Guo T, Chen M-H, Fu S-K, Li Q. Effects of intravenous and intrathecal dexmedetomidine in spinal anesthesia: a meta-analysis. CNS Neurosci Ther. 2013 Nov 14;19(11):897–904. https://doi.org/10.1111/cns.12172 PMid:24118775

10. Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. Reg Anesth Pain Med. 2008 Jan;33(2):159–67. https://doi.org/10.1097/00115550-200803000-00011

11. K.M.HO, Ismail H, Lee KC, Branch R. Use of Intrathecal Neostigmine as an Adjunt to Spinal Medications in Perioperative and Peripartum Analgesia: a Meta- analysis. Anaesth Intensive Care. 2005;volume 33(1):41–53. PMid:15957690

12. Karbasfrushan A, Farhadi K, Amini-Saman J, Bazargan-Hejazi S, Ahmadi A. Effect of intrathecal midazolam in the severity of pain in cesarean section: a randomized controlled trail. Iran Red Crescent Med J. 2012 May;14(5):276–82. PMid:22829986 PMCid:PMC3398634

13. Marinangeli F, Ciccozzi A, Donatelli F, Paladini A, Varrassi G. Clinical use of spinal or epidural steroids. Minerva Anestesiol. 2002;68(7–8):613–20. PMid:12244293

14. Khalili G, Mohsen J, Parvin S, Gholamhossein A. Effects of adjunct intrathecal magnesium sulfate to bupivacaine for spinal anesthesia: A randomized, double-blind trial in patients undergoing lower extremity surgery. J Anesth. 2011;25(6):892–7. https://doi.org/10.1007/s00540-011-1227-z PMid:21928127

15. Jabalameli M, Pakzadmoghadam S. Adding different doses of intrathecal magnesium sulfate for spinal anesthesia in the cesarean section: A prospective double blind randomized trial. Adv Biomed Res. 2012;1(1):7. https://doi.org/10.4103/2277-9175.94430 PMid:23210066 PMCid:PMC3507037

16. 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(3):661–666, table of contents. PMid:12198056

17. Malleeswaran S, Panda N, Mathew P, Bagga R. A randomised study of magnesium sulphate as an adjuvant to intrathecal bupivacaine in patients with mild preeclampsia undergoing caesarean section. Int J Obstet Anesth. 2010;19(2):161–6. https://doi.org/10.1016/j.ijoa.2009.08.007 PMid:20171080

18. Özalevli 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(10):1514–9. https://doi.org/10.1111/j.1399-6576.2005.00793.x PMid:16223399

19. Unlugenc H, Ozalevli M, Gunduz M, Gunasti S, Urunsak IF, Guler T, et al. Comparison of intrathecal magnesium, fentanyl, or placebo combined with bupivacaine 0.5% for parturients undergoing elective cesarean delivery. Acta Anaesthesiol Scand. 2009 Mar;53(3):346–53.

https://doi.org/10.1111/j.1399-6576.2008.01864.x
PMid:19173689

20. Arcioni R, Palmisani S, Tigano S, Santorsola C, Sauli V, Romanò S, 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 Anaesthesiol Scand. 2007 Apr;51(4):482–9.
https://doi.org/10.1111/j.1399-6576.2007.01263.x
PMid:17378788

21. Najafi A, Akbari H, Khajavi M, Etezadi F. Inadvertent intrathecal injection of large dose magnesium sulfate. Saudi J Anaesth. 2013;7(4):464.
https://doi.org/10.4103/1658-354X.121049
PMid:24348302 PMCid:PMC3858701

22. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Vol. 16, Acta anaesthesiologica Scandinavica. Supplementum. 1965.
https://doi.org/10.1111/j.1399-6576.1965.tb00523.x
PMid:5322004

23. Callesen T, Schouenborg L, Nielsen D, Guldager H, Kehlet H. Combined epidural-spinal opioid-free anaesthesia and analgesia for hysterectomy. Vol. 82, British journal of anaesthesia. 1999.
https://doi.org/10.1093/bja/82.6.881

24. Tsai YC, Chu KS. A comparison of tramadol, amitriptyline, and meperidine for postepidural anesthetic shivering in parturients. Vol. 93, Anesthesia and analgesia. 2001.
https://doi.org/10.1097/00000539-200111000-00052

25. 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(1):19–25.
https://doi.org/10.1007/s00540-008-0677-4
PMid:19234817

26. Ascher P, Nowak L. Electrophysiological studies of NMDA receptors. Trends Neurosci. 1987;10(7):284–8.
https://doi.org/10.1016/0166-2236(87)90174-3

27. Woolf CJ, Thompson SWN. 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. 1991;44(3):293–9.
https://doi.org/10.1016/0304-3959(91)90100-C

28. Woolf CJ, Chong MS. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg. 1993;77(2):362–79.
https://doi.org/10.1213/00000539-199377020-00026