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Original Research Article

# A Prospective Randomized Assessment of the Intrathecal Dexmedetomedine and Magnesium Sulfate as Adjuvants to Bupivacaine in Total Hip Replacement

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**Abstract**

**Aim:** The purpose of this study was to evaluate the onset and duration of sensory and motor block as well as perioperative analgesia and adverse effects of dexmedetomidine and magnesium sulfate given intrathecally as adjuvants to bupivacaine in total hip replacement.

**Methods:** The randomized, prospective comparative study was conducted in the Department of Anesthesiology, Patna medical College and Hospital, Patna, Bihar, India. 120 patients, belonging to ASA (American Society of Anesthesiologists) grade I-II scheduled for total hip replacement.

**Results:** 120 patients were enrolled in the study. All the patients completed the study protocol and were included in the data analysis. Thus group B, group M and group D consisted of 40 patients each. There was no significant difference in the demographic data between the three study groups [p >0.05]. The time to reach T10 sensory dermatome, Bromage 3 motor block and regression of the sensory block to L1 dermatome, motor block to Bromage scale 0 were statistically significant between group D, group M and group B. onset of sensory block was rapid and regression of motor block was prolonged significantly in group D. whereas onset of both sensory and motor block was delayed in group M which is highly significant (p <0.001) when compared to group D. regression of sensory dermatome to L1 and motor block to bromage 0 was highly significant (p<0.001) between three study group.

**Conclusion:** Intrathecal DXM supplementation of spinal block seems to be a good alternative to intrathecal Mg as it produces earlier onset and prolonged duration of sensory and motor block without associated significant hemodynamic alterations.

**Keywords:** bupivacaine, Dexmedetomidine, intrathecal, magnesium sulfate

## Introduction

Regional anesthesia (spinal or epidural) is considered to be safer than general anesthesia for lower abdominal and lower limb surgeries. It avoids general anesthesia ‐related problems such as airway manipulation, misplacement of endotracheal tube, hypo or hyperventilation, pulmonary aspiration and metabolic complications. It reduces surgical stress response by attenuating increase in the levels of plasma catecholamines and other hormones, reduces the risk of postoperative thromboembolic events with decreased intraoperative blood loss. In addition to this, regional anesthesia provides intra and postoperative analgesia. [1, 2]

Although various adjuvants have been used to prolong the duration of postoperative analgesia like opioids (morphine, fentanyl, and sufentanil) and other drugs (dexmedetomidine, clonidine, magnesium sulfate, neostigmine, ketamine, and midazolam), but none of the drugs was found to be safer or effective than others in terms of their associated side effects.[3-5]

Magnesium, a non‐competitive N‐methyl ‐D‐aspartate (NMDA) receptor antagonist, whose efficacy or safety as an intrathecal adjuvant has been studied in recent years. Magnesium blocks calcium influx and non‐competitive NMDA channel antagonism. The antinociceptive effect of magnesium seems to be effective in management of chronic and post‐operative pain. The addition of magnesium as intrathecal adjuvant to LA has been reported to improve the post‐operative analgesia. [6, 7]

Dexmedetomidine is a highly selective α‐2 adrenergic agonist which has been used as a premedication as well as an adjuvant to LA agent in spinal anesthesia and general anesthesia. Dexmedetomidine causes sedation, analgesia with minimal hemodynamic changes and respiratory depression. It decreases sympathetic tone with attenuation of the neuroendocrine and hemodynamic response to anesthesia and surgery, enhance the analgesic property of LAs along with reduced anesthetic and opioid analgesic requirement. [8, 9]

Antinociceptive of Mg effects appear to be relevant not only to chronic pain 6 but it also determines, in part, the duration and intensity of postoperative pain.7 These effects are primarily based on the regulation of calcium influx into the cell, i.e. natural physiological calcium antagonism. Mg is a noncompetitive antagonist to NMDA receptors and has the potential to prevent central sensitization from peripheral nociceptive stimulation. Intravenous (i.v.) administration of Mg, even at high doses, is associated with limited passage across the blood–brain barrier. [10] In previous studies, it was demonstrated that intrathecally administered Mg prolonged spinal opioid analgesia both in rats and in humans. [11, 12]

The purpose of this study was to evaluate the onset and duration of sensory and motor block as well as perioperative analgesia and adverse effects of dexmedetomidine and magnesium sulfate given intrathecally as adjuvants to bupivacaine in total hip replacement.

## Methods

The randomized, prospective comparative study was conducted in the Department of Anesthesiology, Patna medical College and Hospital, Patna, Bihar, India for 1 year. 120 patients, belonging to ASA (American Society of Anesthesiologists) grade I-II scheduled for total hip replacement.

Exclusion criteria includes Patients with Hypertension or ischemic heart disease using beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, or noted to have dysrhythmias on the electrocardiogram (ECG),

hypothyroidism, lactating mother ,pregnancy, uncontrolled diabetes or chronic obstructive lung disease ,spinal deformity, height<150 cms and h/o drug allergy. Premedication was avoided in the study group prior to surgery. Standard monitoring was used, including non-invasive arterial blood pressure (BP), ECG, heart rate (HR) and pulse oximetry (SpO2). Preloading was done with 10 ml/kg of crystalloid solution. With the patient in the sitting position, spinal anesthesia was performed at the level of L3-L4 through a midline approach using a 25-gauge Quincke spinal needle which was inserted with the bevel pointing upwards. Patients were randomized into three groups using sealed envelope technique. The dose of hyperbaric 0.5% bupivacaine, 15 mg (3.0 ml) and total spinal volume (3.5 ml) was identical in all study groups. Patients allocated to group B received 3 ml hyperbaric 0.5% bupivacaine 15 mg + 0.5 ml of preservative free normal saline. Patients allocated to group D received 3 ml hyperbaric 0.5% bupivacaine 15 mg + 0.5 ml of preservative free normal saline containing 10 μg dexmedetomidine. Patients allocated to group M received hyperbaric 0.5% bupivacaine 15 mg + 0.5 ml preservative free normal saline containing 50 mg magnesium sulphate. The intrathecal drug formula (total volume 3.5 ml) was prepared by a separate anaesthesiologist under a sterile technique.

The anesthesiologist performing the block was blinded to the study drug and recorded the perioperative data. anaesthetist recorded the baseline value of vital signs (BP, HR, SpO2,) before performing the spinal anesthesia, and once in every 5 minutes inside the O T, then after every 15 minutes in the Post Anesthesia Care Unit (PACU) till the recovery of sensory and motor function. For the purpose of the study, hypotension was defined as a systolic blood pressure of <90 mm Hg and Bradycardia was defined as HR <50 beats/minute. The sensory dermatome level was assessed by pin prick sensation using 23-gauge hypodermic needle along the mid clavicular line bilaterally. The motor dermatome level was assessed according to the modified Bromage scale: Bromage 0, the patient is able to move the hip, knee and ankle; Bromage 1, the patient is unable to move the hip, but is able to move the knee and ankle; Bromage 2, the patient is unable to move the hip and knee, but is able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle. The sensory level and Bromage scale were recorded pre-spinal injection and every two minutes after the spinal injection up to the 10th minute and after that every 3 minutes until the highest dermatome was reached. In the PACU, the sensory level and Bromage scale were recorded every 15 minutes until the patient was discharged from the PACU. All durations were calculated considering the time of spinal injection as time zero. When sensory levels of anesthesia were not equal bilaterally, the higher level was used for the statistical analysis. Patients were discharged from the PACU after complete recovery of sensory and motor function. No premedication was given to the study patients on the previous night of surgery. The level of sedation was evaluated just before surgery, intra operatively and post-operatively every 15 minutes using the Ramsay sedation scales: scale 1 - patient anxious, agitated, or restless; scale 2 - patient cooperative, oriented, and tranquil alert; scale 3, Patient responds to commands; scale 4, Asleep, but with brisk response to light glabellar tap or loud auditory stimulus; scale 5 - Asleep, sluggish response to light glabellar tap or loud auditory stimulus and scale 6- asleep, no response. Patients' neurological assessment was done every day and recorded during hospital stay.

### Statistical analysis

Performed using computer statistical software system SPSS version 16. Data

were expressed as either mean and standard deviation or numbers and percentages. Continuous covariates (age, height, weight and duration of surgery) were compared using analysis of variance (ANOVA). For categorical covariates (gender, ASA class, blood transfusion, nausea/vomiting, hypotension, bradycardia, use of ephedrine, additive analgesia, atropine and type of surgery) a Chi-square test was used, with the p value reported at the 95% confidence interval. For the time to reach T10 dermatome, Bromage 3 scale, and the regression of the sensory block to L1 dermatome and Bromage scale 0, ANOVA test was used to compare the means. The level of significance used was $p<0.05$. The total sample size was calculated to be 120 (40 patients in each group).

## Results

**Table 1: Demographic data (mean±SD) in three study groups**

| Demographic data | B | M | D | P value |
|---|---|---|---|---|
| Age | 38.2 ± 12.5 | 37.4±10.1 | 38.3 ± 11.6 | >0.05 |
| Sex (M/F) | 22/18 | 20/20 | 23/17 | >0.05 |
| Weight (kg) | 64±7 | 65±4 | 63±5 | >0.05 |
| Height | 157±6 | 159±5 | 158±5 | >0.05 |
| ASA Grade I | 35 | 34 | 36 | >0.05 |
| ASA Grade II | 5 | 6 | 4 | >0.05 |

120 patients were enrolled in the study. All the patients completed the study protocol and were included in the data analysis. Thus group B, group M and group D consisted of 40 patients each. There was no significant difference in the demographic data between the three study groups [p >0.05].

**Table 2: Sensory, motor block onset and regression time in minutes (mean ± SD)**

| Group | B | M | D | P value |
|---|---|---|---|---|
| Time to reach T10 | 4.15±1.14 | 6.44±1.32 | 3.27±0.86 | <0.05 |
| Time to Bromage 3 | 4.86±1.30 | 7.33±1.21 | 3.57±1.03 | <0.05 |
| Time to reach L1 | 160.5±21.9 | 236.4+34.5 | 345.5±43.5 | <0.001 |
| Time to Bromage 0 | 153.7±22.5 | 219.0+23.3 | 322.8±38.5 | <0.001 |

The time to reach T10 sensory dermatome, Bromage 3 motor block and regression of the sensory block to L1 dermatome, motor block to Bromage scale 0 were statistically significant between group D, group M and group B. onset of sensory block was rapid and regression of motor block was prolonged significantly in group D. whereas onset of both sensory and motor block was delayed in group M which is highly significant ($p <0.001$) when compared to group D. regression of sensory dermatome to L1 and motor block to bromage 0 was highly significant ($p<0.001$) between three study group.

**Table 3: Perioperative characteristics (mean±SD) in three study groups**

| Perioperative characteristics | B | M | D | P value |
|---|---|---|---|---|
| Intravenous fluid(ml) | 1146.4±231.9 | 1114.0+226.7 | 1173.7±231.9 | >0.05 |
| Duration of surgery | 90.9 ± 22.0 | 92.8±23.5 | 94.0±22.8 | >0.05 |
| Blood Transfusion | 0 | 0 | 0 | >0.05 |
| Additive analgesia | 0 | 0 | 0 | >0.05 |
| PONV | 1 | 0 | 0 | >0.05 |
| Bradycardia | 1 | 1 | 2 | >0.05 |
| Hypotension | 1 | 0 | 1 | >0.05 |
| Atropine | 1 | 1 | 2 | >0.05 |
| Ephedrine | 1 | 0 | 1 | |
| Respiratory depression | 0 | 0 | 0 | >0.05 |
| Shivering | 0 | 0 | 0 | >0.05 |

The total amount of fluids administered following spinal anesthesia, the duration of surgery, amount of ephedrine or atropine, bradycardia, hypotension, need of additive analgesia, blood transfusion, shivering and nausea or vomiting in the intraoperative or in PACU were comparable in the three groups; p>0.05.

## Discussion

DXM reduces opioid and inhalational anesthetic requirements when used intravenously during anesthesia.[13] Compared with clonidine, the affinity of DXM to a-2 receptors has been reported to be 10-times more than clonidine.[14]

Prolongation of duration of spinal block is desirable both for long procedures and for postoperative pain relief. Dexmedetomidine was used in a smaller dose in the spinal block combined with bupivacaine, leading to fast onset and prolongation of block without any significant hemodynamic instability or sedation. [15,16] Largest dose of dexmedetomidine used intrathecally in humans was 10 µg18 .Previous Studies revealed haemodynamic stability with 3 to 10 µg of dexmedetomidine as intrathecal adjuvant. [15-17] Kanazi et al found that the supplementation of bupivacaine (12.0 mg) spinal block with dexmedetomidine (3 µg) produces significantly shorter onset of motor block, and a significantly longer sensory and motor block with preserved haemodynamic stability and lack of sedation. [16] Al-Mustafa et al compared the doses of dexmedetomidine 5 , 10 µg in isobaric bupivacaine 12.5mg (total volume:3 ml) with plain isobaric bupivacaine without premedication and found the effect to be dose dependent on the onset and regression of sensory and motor block with comparable sedation scores among three groups. [17]

On the other hand in magnesium group the onset time to reach sensory dermatomal level T10 and motor blook to bromage 3

was delayed. Ozalevli et al observed asimilar delay in onset of spinal anaesthesia when adding intrathecal magnesium to fentanyl and isobaric bupivacaine. [18] shukla et al found rapid and prolonged duration of surgical anaesthesia in dexmedetomidine group when compared to intrathecal magnesium. They also found that there was a delay in onset of sensory and motor block in magnesium group, but the regression of block was prolonged as compared to plain hyperbaric bupivacaine. [19]

In our study with the usage of 10 μg of intrathecal dexmedetomidine with 15 mg hyperbaric bupivacaine (total volume :3.5 ml) there is a quicker onset and prolong duration of sensory and motor block when compared to magnesium and plain bupivacaine which is similar to shukla et al. [19] The onset of sensory block was delayed in magnesium sulfate group compared to group D and group B, which is similar to the observations made by Ozalevli et al. and malleeswaran et al. [18,20] reason for this delayed onset of action in magnesium group may be due to change in ph and baricity of bupivacaine due to addition of magnesium sulfate .haemodynamic stability was maintained in all the three study groups. Dexmedetomidine has anti shivering effect and there was no incidence of perioperative shivering among study groups. [21]

Mg blocks N-Methyl-D-aspartate (NMDA) channels in a voltage-dependent way and produces a dramatic reduction of NMDA-induced currents. [22] Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters, which bind to the NMDA receptor. Activation of these receptors leads to calcium entry into the cell and initiates a series of central sensitization such as wind-up and long-term potentiation in the spinal cord in the response of cells to prolonged stimuli. [23,24]

## Conclusion

Intrathecal DXM supplementation of spinal block seems to be a good alternative to intrathecal Mg as it produces earlier onset and prolonged duration of sensory and motor block without associated significant hemodynamic alterations. Ten micrograms of DXM as adjuvant to spinal bupivacaine in surgical procedures of long duration has minimal side-effects, and provides excellent quality of postoperative analgesia. Intrathecal Mg also prolongs the duration of spinal analgesia, but this is less than intrathecal DXM and is with a delayed onset. Further studies are required to determine whether larger doses of intrathecal Mg can produce greater potentiation of analgesia and reduce opioid requirements.

## References

1. Kehlet H. The stress response to surgery: release mechanisms and the modifying effect of pain relief. Acta Chirurgica Scandinavica. Supplementum. 1989 Jan 1;550:22-8.
2. Modig J, Borg T, Karlström G, Maripuu E, Sahlstedt B. Thromboembolism after total hip replacement: role of epidural and general anesthesia. Anesthesia and Analgesia. 1983 Feb 1;62(2):174-80.
3. Campbell DC, Banner R, Crone LA, Gore-Hickman W, Yip RW. Addition of epinephrine to intrathecal bupivacaine and sufentanil for ambulatory labor analgesia. The Journal of the American Society of Anesthesiologists. 1997 Mar 1;86 (3): 525-31.
4. Khezri MB, Ghasemi J, Mohammadi N. Evaluation of the analgesic effect of ketamine as an additive to intrathecal bupivacaine in patients undergoing cesarean section. Acta Anaesthesiologica Taiwanica. 2013 Dec 1;51(4):155-60.
5. Yoganarasimha N, Raghavendra TR, Amitha S, Shridhar K, Radha MK. A comparative study between intrathecal clonidine and neostigmine with

intrathecal bupivacaine for lower abdominal surgeries. Indian journal of anaesthesia. 2014 Jan;58(1):43.
6. Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. The Journal of the American Society of Anesthesiologists. 1996 Feb 1;84 (2):3 40-7.
7. Woolf CJ, Thompson SW. 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 Mar 1;44(3):293-9.
8. Kalso EA, Pöyhiä R, Rosenberg PH. Spinal antinociception by dexmedetomidine, a highly selective α2-adrenergic agonist. Pharmacology & toxicology. 1991 Feb;68(2):140-3.
9. Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and peroperative fentanyl. British journal of anaesthesia. 1992 Feb 1;68(2):126-31.
10. Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. Magnesium sulfate does not reduce postoperative analgesic requirements. The Journal of the American Society of Anesthesiologists. 2001 Sep 1;95(3):6 40-6.
11. Kroin JS, McCarthy RJ, Von Roenn N, Schwab B, Tuman KJ, Ivankovich AD. Magnesium sulfate potentiates morphine antinociception at the spinal level. Anesthesia & Analgesia. 2000 Apr 1;90(4):913-7.
12. Buvanendran A, McCarthy RJ, Kroin JS, Leong W, Perry P, Tuman KJ. Intrathecal magnesium prolongs fentanyl analgesia: a prospective, randomized, controlled trial. Anesthesia & Analgesia. 2002 Sep 1;95(3):661-6.
13. Martin E, Ramsay G, Mantz J, Sum-Ping SJ. The role of the α2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. Journal of Intensive Care Medicine. 2003 Jan;18(1):29-41.
14. Post C, Gordh Jr T, Minor BG, Archer T, Freedman J. Antinociceptive effects and spinal cord tissue concentrations after intrathecal injection of guanfacine or clonidine into rats. Anesthesia and analgesia. 1987 Apr 1;66(4):317-24.
15. Kim JE, Kim NY, Lee HS, Kil HK. Effect of intrsthecal dexmedetamidine on low dose bupivacaine spinal anaesthesia in elderly patient undergoing transurethral prostatectomy. Biol Pharm Bull 2013; 36(6):959-65
16. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al-Jazzar MD, Alameddine MM, Al-Yaman R. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand 2006; 50:222-227.
17. Al-Mustafa MM, Abu –Halaweh SA, Aloweidi AS, Mushidi MM, Amman BA, Awwad ZM, Al-Edwan GM, Ramsay MA. Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. Soudi Med j.2009 ;30(3):365-70
18. Özalevli M, Cetin TO, Unlugenc HA, Guler T, Isik G. The effect of adding intrathecal magnesium sulphate to bupivacaine–fentanyl spinal anaesthesia. Acta anaesthesiologica scandinavica. 2005 Nov;49(10):1514-9.
19. Shukla D, Verma A ,Agarwal A, Pandey HD, Tyagi C. Comparitive study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine. Anesthesiol clin pharmacol. 2011; 27 (4):495-99.
20. Malleeswaran S, Ponda N, Malhew P,Bagga R. Magnesium as an intrathecal adjuvant in mild pre

eclampsia . .Int J Obstet Anesth. 2010 ;19:161-6
21. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. The Journal of the American Society of Anesthesio - logists. 1997 Oct 1;87 (4):8 35-41.
22. Liu HT, Hollmann MW, Liu WH, Hoenemann CW, Durieux ME. Modulation of NMDA receptor function by ketamine and magnesium: Part I. Anesthesia & Analgesia. 2001 May 1;92(5):1173-81.
23. Pockett S. Spinal cord synaptic plasticity and chronic pain. Anesthesia & Analgesia. 1995 Jan 1;80(1):173-9.
24. DIANE, S., Baldé, A. K. ., Inapogui, C. B. ., Kéita, A. ., & Diawara, M. . (2022). Functional results of cataract surgery using the phacoemulsification technique "The CADES/O experience. Journal of Medical Research and Health Sciences, 5(9), 2256–2263. https://doi.org/10.52845 /JMRHS/2022-5-9-6