Dexmedetomidine versus magnesium sulfate as an adjuvant to local anesthetics in spinal anesthesia: a meta-analysis of randomized controlled trials

Jinguo Wang¹, Zaitang Wang², Xuesong Song³ and Na Wang³

Abstract

Objective: To compare the efficacy of dexmedetomidine and magnesium sulfate as an adjuvant to local anesthetics in spinal anesthesia.

Methods: A search of PubMed, Medline, Embase, the Cochrane Library, and Google Scholar was performed. Randomized controlled trials comparing the efficacy of dexmedetomidine and magnesium sulfate as a local anesthetic adjuvant in spinal anesthesia were identified. The primary outcome was sensory block duration. The mean difference (MD) or odds ratio along with the 95% confidence interval (CI) was used to analyze the outcomes.

Results: Six studies involving 360 patients were included. Intrathecal dexmedetomidine was associated with a significantly longer sensory block duration (MD = -73.62; 95% CI = -101.09 to -46.15), faster onsets of sensory blockade and motor blockade, and a longer motor block duration than intrathecal magnesium sulfate. There was no significant difference between the groups regarding the rates of hypotension, bradycardia, shivering, and postoperative nausea and vomiting between the groups.

¹Department of Urology, The First Hospital of Jilin University, Changchun, Jilin, China
²Department of Taxation, School of Public Economics and Administration of Shanghai University of Finance and Economics, Changchun, Jilin, China
³Department of Anesthesiology, The First Hospital of Jilin University, Changchun, Jilin, China

We hereby certify that this paper consists of original, unpublished work that is not under consideration for publication elsewhere. The abstract has not been presented at any conference proceedings. All authors read and approved the final manuscript.

Corresponding author:
Na Wang, Department of Anesthesiology, The First Hospital of Jilin University, No. 1 Xinmin Street, Changchun, Jilin 130021, China.
Email: wangna080613@163.com
Conclusions: Dexmedetomidine is superior to magnesium sulfate as an adjuvant to local anesthetics in spinal anesthesia because of its more rapid onset and longer duration of spinal block without significant adverse effects.

Keywords
Meta-analysis, dexmedetomidine, magnesium, spinal anesthesia, adjuvant, sensory block, randomized controlled trial

Introduction
Spinal anesthesia is a common and reliable anesthetic technique, but it has the disadvantage of a limited duration of action. Therefore, appropriate adjuvants are added to local anesthetics during spinal anesthesia to enhance the blockage quality and extend the block duration.1,2

N-methyl-D-aspartate (NMDA) receptors antagonists and α2 adrenergic agonists can be used as adjuvants in spinal anesthesia.1,2 Magnesium sulfate exhibits analgesic properties, primarily because it can block calcium influx into cells and antagonize NMDA receptors in the central nervous system (CNS). When injected intrathecally, magnesium exerts stronger effects on spinal cord NMDA receptors.3–6

Dexmedetomidine can act as an α2-adrenoceptor agonist in the peripheral and CNS. This analgesic effect of intrathecal dexmedetomidine occurs through inhibition of the release of C-fiber transmitters and hyperpolarization of the postsynaptic dorsal horn neurons, which can explain the prolonged duration of spinal block when dexmedetomidine was added to intrathecal anesthetics.7,8

Several randomized controlled trials (RCTs) have compared the analgesic effect of intrathecal dexmedetomidine and intrathecal magnesium sulfate in recent years.9–11 We decided to perform a meta-analysis to formally compare the efficacy of these agents as local anesthetic adjuvants in spinal anesthesia using a large sample size.

Methods
This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,12 and we did not register our study with PROSPERO. A literature search of PubMed, Medline, Embase, the Cochrane Library, and Google Scholar was performed from inception up to December 2019 using the following terms: intrathecal, anesthesia, spinal injections, magnesium, magnesium sulfate, dexmedetomidine, Dex, clinical trial, and randomized controlled trial. There were no language restrictions.

Inclusion criteria
The inclusion criteria were as follows: 1) adult patients who underwent surgery under spinal anesthesia; 2) dexmedetomidine and magnesium were compared as adjuvants to local anesthetics; and 3) the study was an RCT.

Exclusion criteria
Animal studies, conference reports, correspondences, or editorials were excluded.
Data extraction

Two researchers chose eligible clinical trials independently. The titles and abstracts of the initially selected articles were examined. The citations of these articles were also obtained and examined to identify eligible studies. Thereafter, the references of the identified papers were searched manually to find additional eligible papers.

Two authors independently analyzed the quality of the eligible RCTs using the Jadad score (a minimum of 3 points was required) and the Cochrane Collaboration guidelines. Any disagreement was resolved by a third researcher.

Two authors independently extracted relevant data from the included RCTs. Any disagreement was resolved by a third author. If the included RCTs contained more than two groups, data were extracted only for the intrathecal dexmedetomidine and intrathecal magnesium groups. The primary endpoint was sensory block duration in the intrathecal dexmedetomidine and intrathecal magnesium groups.

Statistical analysis

Statistical analysis was conducted using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). The mean difference (MD) or odds ratio along with the 95% confidence interval (CI) was used to analyze the outcomes. Leave-one-out sensitivity analysis was performed by iteratively removing one study at a time if a high level of heterogeneity was detected ($I^2 > 50\%$). $P < 0.05$ denoted statistical significance.

Results

The search flowchart was presented in Figure 1. Two hundred fifty-four records were initially identified in the literature search. Of these, 242 studies were excluded after screening the abstracts. The full texts of 12 articles were found and examined, after which six more articles were excluded. Overall, six RCTs involving a total of 360 patients were identified for the final analysis. The characteristics of the eligible RCTs are displayed in Table 1. All six articles had intermediate to high Jadad scores (Table 1). The risk-of-bias plot was created using Review Manager 5.3 (Figure 2).

Sensory block duration

Five studies reported the sensory block duration after intrathecal injection. Patients in the intrathecal dexmedetomidine group had a longer sensory block duration ($\text{MD} = -73.62;\ 95\%\ \text{CI} = -101.09\text{ to } -46.15,\ P < 0.00001,\ I^2 = 92\%$, Figure 3).
Table 1. Characteristics of the included studies.

| Author       | Date | Jadad score | Dosage of the study drugs | Study type | Sample size | Patient age | ASA status | Surgical setting | Local anesthetics for spinal anesthesia | Outcomes measures |
|--------------|------|-------------|---------------------------|------------|-------------|-------------|------------|------------------|----------------------------------------|-------------------|
| Omar         | 2019 | 5           | Dex: 5 μg; M: 25 mg        | RCT        | 35/35/35    | 20–60 years | I–II       | Uroscopic surgery | 12.5 mg of hyperbaric bupivacaine        | 1, 2, 3, 4, 5, 6, 7, 8, 9 |
| Mostafa      | 2019 | 5           | Dex: 5 μg; M: 25 mg        | RCT        | 30/30/30    | 20–45 years | I–II       | Caesarean delivery | 12.5 mg of hyperbaric bupivacaine        | 1, 2, 3, 4 |
| Makhni       | 2017 | 3           | Dex: 10 μg; M: 75 mg       | RCT        | 25/25       | 20–65 years | I–II       | Infraumbilical surgeries | 3 mL of 0.75% isobaric ropivacaine          | 1, 2, 3, 4, 5, 6, 9 |
| SUNIL        | 2013 | 4           | Dex: 10 μg; M: 50 mg       | RCT        | 30/30/30    | 18–45 years | I–II       | Lower limb surgeries | 15 mg of hyperbaric bupivacaine          | 1, 2, 3, 4, 5, 6, 9 |
| Shukla       | 2011 | 4           | Dex: 10 μg; M: 50 mg       | RCT        | 30/30/30    | 18–45 years | I–II       | Lower abdominal and lower limb procedures | 15 mg of hyperbaric bupivacaine          | 1, 2, 3, 4 |
| Farooq       | 2017 | 4           | Dex: 10 μg; M: 50 mg       | RCT        | 30/30/30    | 18–65 years | I–II       | Lower abdominal and lower limb surgery | 15 mg of hyperbaric bupivacaine          | 1, 2 |

Dex, dexmedetomidine; M, magnesium; S, saline; RCT, randomized controlled trial; ASA, American Society of Anesthesiologists. 1: Onset of sensory blockade; 2: Sensory block duration; 3: Onset of motor blockade; 4: Motor block duration; 5: Postoperative pain intensity; 6: Sedation score; 7: Nausea and vomiting; 8: Shivering; 9: Hypotension and bradycardia; 10: Postoperative rescue analgesics.
Sensitivity analysis was conducted to assess the reliability of the result by removing each RCT individually, and the results did not change (Table 2).

**Onset of sensory blockade**

All six included studies compared the onset of sensory blockade. Patients receiving intrathecal dexmedetomidine had a significantly faster onset of sensory blockade (MD = 2.77; 95% CI = 1.77–3.77, \( P < 0.00001, I^2 = 96\% \)) than patients receiving intrathecal magnesium (Figure 4). Leave-one-out sensitivity analysis did not result in changes of the results.

**Onset and duration of motor blockade**

The onset of motor blockade were assessed in five studies (300 patients), and the motor block duration was reported in four studies involving 240 patients. Patients receiving intrathecal dexmedetomidine had a significantly faster onset of motor blockade (MD = 3.07; 95% CI = 2.02–4.11, \( P < 0.00001, I^2 = 94\% \), Figure 5) and a longer motor block duration (MD = −61.58; 95% CI = −107.76 to −15.41, \( P = 0.009, I^2 = 97\% \), Figure 6) than patients receiving intrathecal magnesium. The results did not differ when
Table 2. Sensitivity analysis of the primary outcome: Sensory block duration.

| Author       | MD      | 95% CI lower limit | 95% CI upper limit | Z value | I²   | P     |
|--------------|---------|--------------------|--------------------|---------|------|-------|
| Omar 2019    | -78.08  | -116.14            | -40.02             | 40.02   | 94%  | <0.0001 |
| Mostafa 2019 | -83.50  | -107.38            | -59.62             | 60.85   | 82%  | <0.00001 |
| Makhni 2017  | -71.51  | -103.90            | -39.12             | 40.33   | 93%  | <0.00001 |
| SUNIT 2013   | -64.06  | -87.73             | -40.39             | 50.30   | 87%  | <0.00001 |
| Shukla 2011  | -70.72  | -101.88            | -39.57             | 40.45   | 93%  | <0.00001 |

The results are presented after the indicated study was excluded in the leave-one-out sensitivity analysis. MD, mean difference; CI, confidence interval.

Figure 4. Forest plot for the onset of sensory block in minutes. SD, standard deviation; CI, confidence interval; IV, inverse variance.

Figure 5. Forest plot for the onset of motor block in minutes. SD, standard deviation; CI, confidence interval; IV, inverse variance.

Figure 6. Forest plot for the motor block duration in minutes. SD, standard deviation; CI, confidence interval; IV, inverse variance.
conducting the leave-one-out sensitivity analysis.

Side effects
Two studies assessed the rates of hypotension, bradycardia, shivering, and postoperative nausea and vomiting. No significant differences in the rates of any of these adverse events were noted between the groups (Figure 7).

Discussion
This study demonstrated that intrathecal dexmedetomidine is associated with longer durations of sensory and motor block and shorter onsets of sensory and motor block than intrathecal magnesium sulfate without an increased risk of adverse effects. Therefore, dexmedetomidine is superior to magnesium sulfate as a local anesthetic adjuvant for spinal anesthesia.

Dexmedetomidine is a highly selective \( \alpha_2 \)-adrenoceptor agonist. The analgesic effect of intrathecal dexmedetomidine occurs through the inhibition of C-fiber transmitter release and hyperpolarization of postsynaptic dorsal horn neurons. The mechanism by which dexmedetomidine prolongs spinal block as a local anesthetic

![Figure 7. Forest plot for the incidence of side effects. CI, confidence interval; M-H, Mantel–Haenszel.](image-url)
adjuvant is unclear. The synergistic effect between the local anesthetic and z2-adrenoceptor agonist may contribute to this phenomenon. Local anesthetics and z2-adrenoceptor agonists have different mechanisms of analgesia. Local anesthetics block sodium channels, whereas z2-adrenoceptor agonists bind to pre-synaptic C fibers and postsynaptic dorsal horn neurons to produce analgesic effects.

Magnesium can inhibit calcium influx into cells and antagonize NMDA receptors, which may determine the duration of acute pain.4,5 Kroin et al.19 reported that intrathecal magnesium enhanced the analgesic effect of opioids for acute pain in rat models.

The results of this meta-analysis did not reveal statistically significant differences between the rates of hypotension, bradycardia, shivering, and postoperative nausea and vomiting between the dexmedetomidine and magnesium groups.

There was a high level of heterogeneity for some outcomes. Therefore, more high-quality RCTs with large sample sizes are needed. However, the results of this meta-analysis were not changed in the leave-one-out sensitivity analysis, illustrating that the meta-analysis results were not driven by any single study.

Conclusion
Dexmedetomidine is superior to magnesium sulfate as a local anesthetic adjuvant in spinal anesthesia because of its more rapid onset and longer duration of spinal block without significant adverse effects in patients.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD
Na Wang https://orcid.org/0000-0002-8312-9787

Supplemental material
Supplemental material for this article is available online.

References
1. Koyyalamudi V, Sen S, Patil S, et al. Adjuvant agents in regional anesthesia in the ambulatory setting. Curr Pain Headache Rep 2017; 21: 6.
2. Emelife PI, Eng MR, Menard BL, et al. Adjunct medications for peripheral and neuraxial anesthesia. Best Pract Res Clin Anaesthesiol 2018; 32: 83–99.
3. Albrecht E, Kirkham KR, Liu SS, et al. The analgesic efficacy and safety of neuraxial magnesium sulphate: a quantitative review. Anaesthesia 2013; 68: 190–202.
4. Iseri LT and French JH. Magnesium: nature’s physiologic calcium blocker. Am Heart J 1984; 108: 188–193.
5. Woolf CJ and 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; 44: 293–299.
6. Feria M, Abad F, Sanchez A, et al. Magnesium sulphate injected subcutaneously suppresses autotomy in peripherally deafferented rats. Pain 1993; 53: 287–293.
7. Lawhead RG, Blaxall HS and Bylund DB. Alpha-2A is the predominant alpha-2 adrenergic receptor subtype in human spinal cord. Anesthesiology 1992; 77: 983–991.
8. Asano T, Dohi S, Ohta S, et al. Antinoceception by epidural and systemic alpha(2)-adrenoceptor agonists and their binding affinity in rat spinal cord and brain. Anesth Analg 2000; 90: 400–407.
9. Omar H, Aboella WA, Hassan MM, et al. Comparative study between intrathecal dexmedetomidine and intrathecal magnesium sulfate for the prevention of post-spinal anaesthesia shivering in uroscopic surgery; (RCT). *BMC Anesthesiol* 2019; 19: 190.

10. Mostafa MF, Herdan R, Fathy GM, et al. Intrathecal dexmedetomidine versus magnesium sulphate for postoperative analgesia and stress response after caesarean delivery; randomized controlled double-blind study. *Eur J Pain* 2019; 24: 182–191.

11. Makhni R, Attri JP, Jain P, et al. Comparison of dexmedetomidine and magnesium sulfate as adjuvants with ropivacaine for spinal anesthesia in infraumbilical surgeries and postoperative analgesia. *Anesth Essays Res* 2017; 11: 206–210.

12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; 8: 336–341.

13. Jadad AR, Moore A, Carroll D, et al. Assessing the quality of reports on randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.

14. Higgins JPT and Green S. Cochrane handbook for systematic reviews of interventions. *The Cochrane Collaboration* 2011; version 5.1.0. [cited 2013 May 7]. www.cochrane-handbook.org.

15. Sunil BV and Sahana KS. Comparison of dexmedetomidine and magnesium sulfate as adjuvants with hyperbaric bupivacaine for spinal anesthesia. A double blind controlled study. *J Med Sci Clin Res* 2013; 1: 117–141.

16. Shukla D, Verma A, Agarwal A, et al. Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvant to bupivacaine. *Anesthesiol Clin Pharmacy* 2011; 27: 495–499.

17. Farooq Z and Gupta N. Sulphate and dexmedetomidine used intrathecally as adjuvant to bupivacaine: a study. *Int J Med Res Health Sci* 2017; 6: 42–46.

18. Fairbanks CA and Wilcox GL. Spinal antinociceptive synergism between morphine and clonidine persist in mice made acutely or chronically tolerant to morphine. *J Pharmacol Exp Ther* 1999; 288: 1107–1116.

19. Kroin JS, McCarthy RJ, Von Roenn N, et al. Magnesium sulfate potentiates morphine antinociception at the spinal level. *Anesth Analg* 2000; 90: 913–917.