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Research Article

Dexmedetomidine versus Magnesium Sulfate as Adjuvants in Orthopedic Surgery: A Randomized Controlled Trial. A Head-to-Head Comparison

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ABSTRACT

Background: The optimal adjuvant for epidural anesthesia in orthopedic surgery remains controversial. Although epidural use has declined in some ERAS protocols, it remains valuable for prolonged procedures, patients with contraindications to spinal anesthesia, and resource-limited settings. No randomized trial has directly compared dexmedetomidine (Dex) and magnesium sulfate ($MgSO_4$) as epidural adjuvants specifically in lower limb orthopedic procedures. We compared their efficacy as adjuvants to bupivacaine.

Methods: We randomized 100 ASA I-II patients who received epidural bupivacaine (15 mg) to either $MgSO_4$ 50 mg or dexmedetomidine 5 µg. The primary outcome was the sensory block duration, and we also assessed sensory onset time and motor block parameters, analgesic requirements, pain scores, time to first mobilization, and adverse events as secondary outcomes.

Results: Group D demonstrated significantly longer sensory block duration (mean difference 64 minutes; 95% CI [47,81]; $p<0.001$), approaching the 60-minute clinically significant threshold. Group D had faster sensory onset (mean difference −4.2 minutes; $p<0.001$) and lower 24-hour pethidine requirement (mean difference −35 mg; $p=0.003$). An exploratory observation was sensory prolongation without a statistically significant motor block increase (225 vs. 210 min, $p=0.12$), suggesting a potential sensory-sparing effect requiring validation. Group D had lower pain scores at 6 and 12 hours ($p<0.001$), and shorter time to first mobilization (median 8.5 vs. 11.2 hours; $p=0.02$), and magnified benefits in the trauma subgroup (n=40, post-hoc). Bradycardia was more common in Group D (8% vs. 2%; $p=0.04$), but other adverse events were comparable.

Conclusion: Dexmedetomidine provides a longer sensory block, faster onset, superior analgesia, reduced opioid consumption, and earlier mobilization compared to $MgSO_4$ as an epidural adjuvant for lower limb orthopedic surgery, but with a higher bradycardia risk. The sensory-sparing effect and trauma subgroup benefit require prospective validation.

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Introduction

Epidural anesthesia is an established standard technique for orthopedic surgery in the lower limb, valued for its ability to provide effective intraoperative anesthesia and extended postoperative analgesia. However, its use has declined in some ERAS (Enhanced Recovery After Surgery) protocols, where spinal anesthesia and peripheral nerve blocks are increasingly preferred alternatives. It remains clinically relevant in several scenarios:

1- prolonged surgical procedures requiring intraoperative extension of anesthesia;
2- contraindications to spinal anesthesia (such as spinal stenosis, prior spinal surgery, and anatomical abnormalities);
3- cases where postoperative epidural analgesia is planned for the first 24-48 hours;
4- resource-limited settings where sophisticated peripheral nerve block equipment may not be readily available [1].

Though bupivacaine is still a popular choice for epidural blocks because of its reliable sensory and motor blockade [2], physicians frequently look for adjuvant medications to solve its two main drawbacks: the slow onset of action and relatively brief duration when used alone [3].

Magnesium sulfate ($MgSO_4$) and dexmedetomidine (Dex) are two such adjuvants whose possibilities to intensify the anesthetic effectiveness and duration of analgesia of the epidural blockade have been noted. Magnesium sulfate, an NMDA receptor antagonist, modulates nociceptive transmission by blocking calcium influx and reducing central sensitization. While it has been shown to prolong analgesia, its effects on onset time are inconsistent [4-5].

The selective α_2-adrenergic agonist dexmedetomidine, however, exerts its analgesic effects through spinal and supraspinal mechanisms. When used as an adjunct in neuraxial anesthesia, Dex has been shown to speed sensory block onset and prolong postoperative pain relief through mechanisms such as inhibition of substance P release and hyperpolarization of dorsal horn neurons [6-7].

Although both adjuvants have been individually studied, the existing literature lacks a direct, randomized, head-to-head comparison of $MgSO_4$ versus Dex as epidural adjuvants specifically in lower limb orthopedic surgery. Most previous studies have compared each adjuvant against a placebo or other drugs (e.g., clonidine, fentanyl) in different neuraxial or peripheral block settings.

While Shafi et al. (2023) compared these agents in a mixed surgical population, their study did not report on sensory-motor dissociation, trauma subgroup effects, or functional outcomes such as time to mobilization [8]. Consequently, evidence of high quality is lacking to guide anesthesiologists in choosing between these two widely available options for epidural anesthesia in orthopedic patients. This knowledge gap is clinically relevant because orthopedic procedures often require prolonged postoperative analgesia due to substantial tissue trauma and bone involvement [9].

Regarding the choice of magnesium sulfate as a comparator, we acknowledge that intravenous magnesium has demonstrated analgesic effects. However, epidural magnesium continues to be used in clinical practice, with approximately 35% of anesthesiologists in some regions reporting its use as a bupivacaine adjuvant for orthopedic procedures. The epidural route offers theoretical advantages through direct action on spinal NMDA receptors and dorsal horn neurons, potentially providing more targeted analgesia with lower systemic doses [10].

Our study is designed to guide clinicians who have already decided to use an epidural adjuvant, providing direct comparative evidence for choosing between these two available options.

This investigation directly compared the efficacy of the addition of magnesium sulfate ($MgSO_4$) and dexmedetomidine (Dex) to bupivacaine for epidural anesthesia in lower limb orthopedic surgery. By providing the first randomized evidence for this specific comparison, with detailed characterization of block characteristics and functional outcomes, the results of this research will help to support evidence-based decision-making in picking the most effective adjuvant for epidural anesthesia in orthopedic patients, therefore improving surgical outcomes and patient satisfaction.

Methods

This prospective, double-blind, randomized clinical trial was conducted with two parallel active comparator groups. All study procedures were performed in the operating room and post-anesthesia care unit of Imam Khomeini Hospital, Ahvaz, Iran, during 2024.

Ethical approval: This was gotten from the Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1401.204) on September 25, 2019. The study was registered with the Iranian Clinical Trials Registry (IRCT20231114060049N1) on November 14, 2023, prior to patient enrollment. Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study participants: Age 18–65 years, American Society of Anesthesiologists physical status (ASA) I-II, candidate for unilateral lower limb orthopedic surgery, and no contraindications to epidural anesthesia were inclusion criteria.

History of allergy to any study medication, addiction, chronic pain syndrome, and contraindication of central neuraxial block were factors for exclusion from the study.

Randomization and Blinding

An independent biostatistician used G*Power to generate a 1:1 randomized sequence with fixed block sizes of 4. An uninvolved research assistant prepared opaque, numbered, tamper-evident envelopes with the group allocations. The envelopes were stored securely and were only opened by the administering anesthesiologist after the patient had provided written informed consent and was positioned for the neuraxial block, immediately prior to drug preparation. This process ensured that the allocation was concealed from the investigators enrolling participants and from the patients until the moment of the intervention.

The patients, anesthesiologists performing the intraoperative management and postoperative assessments, data collectors, and statisticians were all blinded to the group assignments. Both adjuvants (50 mg $MgSO_4$ in 1 mL and 5 µg dexmedetomidine in 1 mL) were clear, colorless solutions and were drawn into identical 1 mL syringes labeled only with the patient's study identification number. These syringes were then handed to the procedural anesthesiologist, who added the contents to the standardized dose of bupivacaine. The final drug was identical in volume and appearance between the two groups.

Procedure

Patients fasted according to guidelines. Patients received IV Ringer's solution (7 ml/kg) following establishing intravenous access in the operating room. After that, a 1–1.5 mg IV midazolam was administered for anxiolysis before epidural anesthesia.

Baseline vital signs, including heart rate (HR), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2), were recorded. Routine monitoring with electrocardiography (ECG), non-invasive blood pressure (NIBP), and pulse oximetry was also established.

A sitting or lateral decubitus position, depending on patient comfort, was chosen to perform the procedure. After antiseptic skin preparation and sterile draping, the epidural space was identified at the L3–L4 or L4–L5 interspace using an 18G Tuohy needle and the loss-of-resistance-to-saline technique.

For epidural administration, Group M (n=50) received 14 mL of 0.5% plain bupivacaine combined with 50 mg of preservative-free magnesium sulfate (diluted in 1 mL of 0.9% saline). Group D (n=50) received 14 mL of 0.5% plain bupivacaine combined with 5 µg of preservative-free dexmedetomidine (diluted in 1 mL of 0.9% saline). In both groups, the total volume injected was 15 mL. (The dose of 5 µg dexmedetomidine was selected based on the meta-analysis by Zhang et al. [24], which identified this dose as optimal for epidural use, balancing analgesic efficacy with an acceptable bradycardia profile (approximately 8%). The 50 mg dose of magnesium sulfate was chosen based on previous randomized trials [4,10] demonstrating effective analgesia prolongation without excessive motor block or hypotension). Following epidural block placement, all patients received a propofol infusion at 25–50 µg/kg/min, titrated to maintain a Ramsay Sedation Scale (RSS) score of 2–3 (2 = cooperative, oriented, and tranquil; 3 = responsive to commands only) [11]. RSS was assessed every

10 minutes, and the infusion rate was adjusted in

10 µg/kg/min increments to maintain the target sedation level.

All patients received Ringer's solution intraoperative (8 ml/kg/h). Hypotension (decrease in mean arterial pressure (MAP) to <60 mmHg) was treated with 5 mg boluses of intravenous ephedrine.

Intravenous atropine in 0.5 mg boluses was injected if bradycardia (HR < 45 bpm) was observed.

Intravenous pethidine 25 mg was administered as a standard analgesic once the VAS pain score was greater than 4 in the postoperative period. Pethidine remains the standard rescue opioid in our center due to its availability and cost-effectiveness in our resource-limited setting, though we acknowledge that other opioids such as morphine or fentanyl are preferred in many international guidelines. We recorded the time to first saving analgesia and the total pethidine consumption over 24 hours.

Intravenous ondansetron 4 mg was administered for postoperative nausea and vomiting.

Vital signs were checked every 5 minutes for the first 30 minutes and then every 15 minutes.

The primary outcome was sensory block duration, which was measured bilaterally using a short beveled 26G sterile hypodermic needle along the mid-clavicular line, with the time to reach the T10 level recorded. Motor block was assessed using the Bromage scale (0–3): 0 = no motor block; 1 = unable to raise the extended leg but can move knees and feet; 2 = unable to raise the extended leg or move the knee but can move feet; 3 = complete motor block [12].

Secondary outcomes include hemodynamic parameters, postoperative analgesic requirements, and pain scores (postoperative analgesia was standardized; upon patient request or a VAS score >4, 25 mg boluses were given intravenously). Pethidine was given as rescue medication, time to first postoperative mobilization (the time from the end of surgery to the patient's first attempt to stand and ambulate with assistance, assessed every

4 hours by a blinded physiotherapist), and the other side effects: Bradycardia: HR < 45 bpm. Hypotension: MAP < 60 mmHg. Respiratory Depression: RR < 8 per minute and/or SpO_2 < 92% on room air. Nausea/Vomiting: Any report of nausea or episode of vomiting. Pruritus: Any

patient report of itching. Shivering: Observable shivering of any intensity. The time of onset (intraoperative vs. postoperative), severity (e.g., requiring intervention), and management for each event were recorded. All adverse events were assessed by the blinded anesthesiologist for relatedness to the study intervention. Block failure was predefined as: (1) failure to achieve a sensory block at or above the T10 dermatome within 30 minutes of epidural injection; (2) inadequate surgical anesthesia requiring supplemental local infiltration or conversion to general anesthesia; or (3) patient-reported pain requiring intraoperative rescue analgesia despite confirmation of catheter position. In the event of block failure, the planned management was to administer supplemental local anesthetic via the epidural catheter (if appropriate) or convert to general anesthesia with endotracheal intubation. No block failures occurred in either group. We recognized both the time to first rescue pain medication (triggered by VAS ≥4) and the 24-hour cumulative pethidine dose (mg).

Sample sizes

Computed utilizing G*Power 3.1 based on pilot data (mean difference in sensory duration = 60 min, SD = 45, α = 0.05, power = 90%). Inflated to 50/group for dropouts; required sample size was 45 per group.

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of continuous data. Normally distributed variables were compared between groups using independent t-tests and expressed as mean ± standard deviation (SD). Non-normally distributed continuous variables were analyzed using the Mann-Whitney U test and presented as median [interquartile range, IQR]. Categorical variables were compared using the chi-square (χ^2) test or Fisher's exact test, as appropriate.

All statistical analyses were performed using SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). A two-tailed P value <0.05 was considered statistically significant.

For repeated VAS pain score measurements, a linear mixed model was used to evaluate group-by-time interaction, with post-hoc pairwise comparisons performed as appropriate.

Results

The study selected 126 patients for eligibility, with 26 excluded (18 were ineligible, 5 refused consent, and 3 had medical contraindications to epidural anesthesia). Equal randomization of the final 100 patients produced two groups of 50 each. There were no dropouts, as all randomized individuals fully completed the study (Figure 1). The groups were comparable at baseline, as reflected by the absence of significant demographic or clinical differences (all p > 0.05; (Table 1)). Results of the sensory block were as follows: Onset at T10: significantly faster for Group D (8.2±1.5 vs. 12.4±2.1 min; p<0.001; Δ=4.2 min, 95% CI: 3.1–5.3). Time to maximal level (T6)**:** significantly shorter for Group D (14.8±2.4 vs. 18.6±3.1 min; p<0.001). Total duration: significantly longer for Group D (342±45 vs. 278±38 min; p<0.001; ES=1.52). The 64-minute absolute difference (95% CI: 47–81) nears the 60-minute threshold considered clinically meaningful for postoperative pain control.

Motor block: Onset**:** comparable between groups (16.3±2.8 vs. 18.6±3.2 min; p=0.07). Duration: longer in Group D (225±40 vs. 210±32 min), but this was not significant (p=0.12). Interpretation**:** The selective prolongation of sensory over motor blockade suggests a potential sensory-sparing profile, though this should be viewed as hypothesis-generating since the trial was not powered for this specific comparison. Postoperative Analgesia: Patients in Group D required their first rescue dose significantly later than those in the comparison group (342 ± 45 vs. 278 ± 38 min; p < 0.001). 24-h Opioid (Pethidine) Consumption: Group D required less pethidine (85 ± 22 mg vs. 120 ± 30 mg; p=0.003). Pain scores at different times are shown in (Table 2). Functional Outcome: First mobilization occurred a median of 2.7 hours earlier in Group D (8.5 hours [IQR: 7.2–10.1]) than in the control group (11.2 hours [IQR: 9.0–13.5]), a difference that was statistically significant (p = 0.02), suggesting that improved postoperative analgesia may facilitate earlier mobilization under ERAS protocols. Safety and Adverse Events:

The frequency of bradycardia in Group D remained significantly higher (8% vs. 2%; p = 0.04). All episodes of bradycardia occurred intraoperative, were assessed as definitely related to the study drug, and were successfully resolved with a single 0.5 mg bolus of intravenous atropine. No patient required additional doses or developed hemodynamic instability.

There were no instances of respiratory depression (0% in both groups; 95% CI for single proportion [0.0%, 7.1%] per group), defined as SpO_2 < 92% or a respiratory rate of < 8 breaths per minute. The frequencies of adverse events—specifically nausea/vomiting, hypotension, and pruritus—were statistically equivalent across the study groups.

All cases of hypotension were managed with ephedrine boluses, and nausea/vomiting was treated with ondansetron (Table 3).

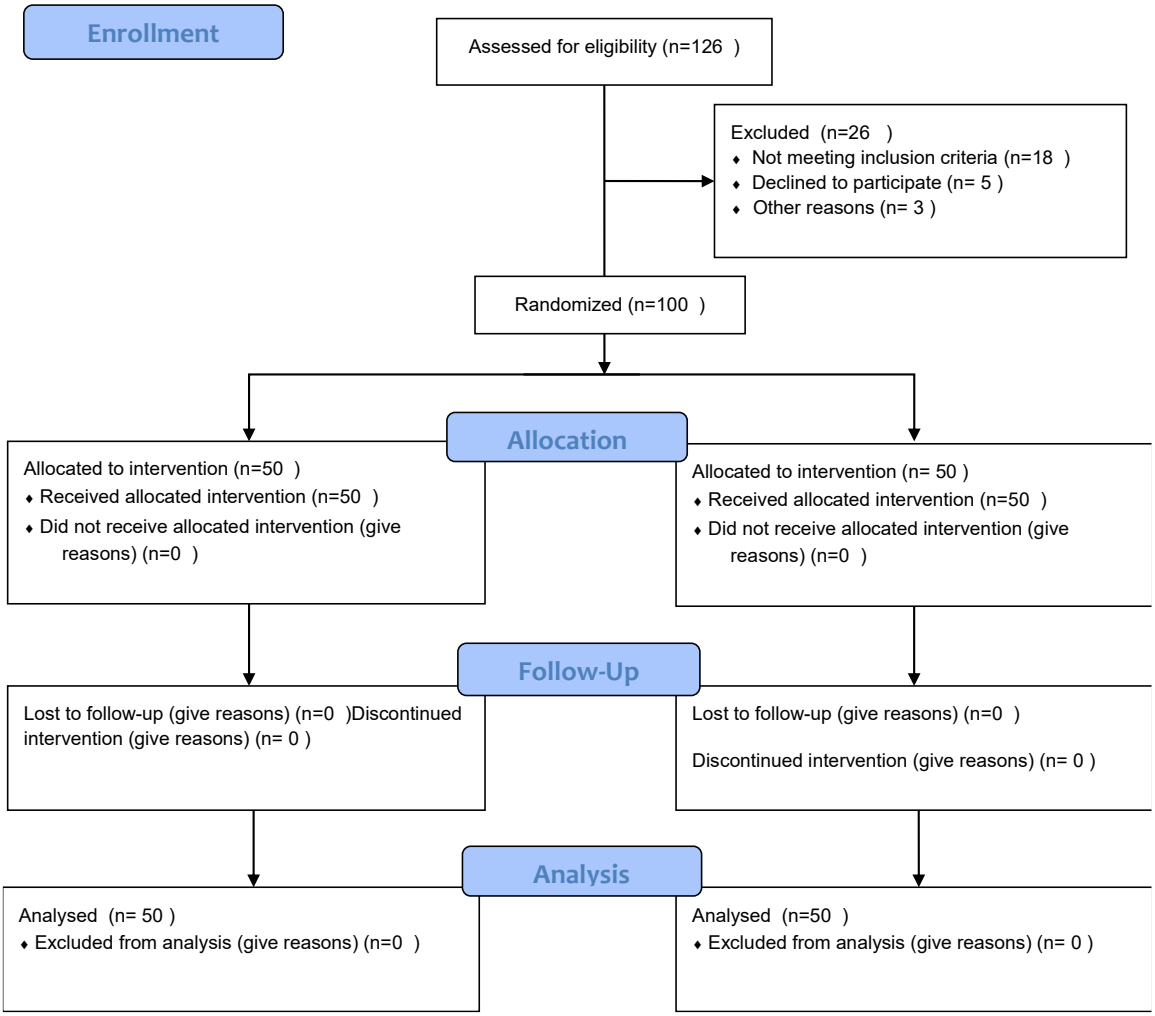

Figure 1- The CONSORT Flow Diagram: The diagram shows the flow of participants through the trial, including the number of patients assessed for eligibility (n=126), excluded (n=26), randomized (n=100), and analyzed in each group (n=50 per group). No patients were lost to follow-up or discontinued the intervention

Table 1- Patient Baseline Demographics and Clinical Characteristics

Variables	M Group (50)	D Group (50)	P value
Age (years)	48.2 ± 12.5	50.1 ± 11.8	0.42
Sex (Male)	28	30	0.69
Weight (kg)	68.5 ± 9.2	70.1 ± 8.7	0.35
ASA Status (I/II)	32/18	34/16	0.71
Type of Surgery			0.82
Total Knee Arthroplasty	18	20	
Hip Arthroplasty	12	10	
Fracture Fixation	20	20	

Data presented as mean ± standard deviation (SD) or number (n). M Group: Magnesium Sulfate + Bupivacaine; D Group: Dexmedetomidine + Bupivacaine. ASA: American Society of Anesthesiologists. P values from independent t-tests (continuous) or χ^2 tests (categorical)

Table 2- Pain Scores undergoing Visual Analog Scale (VAS)

Time Point	M Group (50)	D Group (50)	Mean Difference [95% CI]	P value
1h Postop	2.1 ± 0.8	1.8 ± 0.6	-0.3 [-0.6, 0.1]	0.12
6h Postop	3.5 ± 1.1	2.4 ± 0.9	-1.1 [-1.5, -0.7]	<0.001
12h Postop	4.2 ± 1.3	3.1 ± 1.0	-1.1 [-1.6, -0.6]	<0.001

Data presented as mean ± standard deviation (SD). M Group: Magnesium Sulfate + Bupivacaine; D Group: Dexmedetomidine + Bupivacaine. VAS: Visual Analog Scale (0-10). P values from exploratory post-hoc comparisons following significant group-by-time interaction in a linear mixed model ($F(2,196) = 8.74$, $p < 0.001$).

Table 3- Comprehensive Analysis of Adverse Events (Harms)

Adverse Event	Definition	M Group (50)	D Group (50)	P value	Onset Time	Management
Bradycardia	HR < 45 bpm	1 (2%)	4 (8%)	0.04	Intraoperative	Atropine 0.5 mg IV
Hypotension	MAP < 60 mmHg	2 (4%)	3 (6%)	0.50	Intraoperative	Ephedrine 5 mg IV
Nausea/Vomiting	Patient report/emesis	5 (10%)	3 (6%)	0.34	Postoperative	Ondansetron 4 mg IV
Pruritus	Patient report of itching	2 (4%)	0 (0%)	0.24	Postoperative	None required
Shivering	Observable shivering	1 (2%)	0 (0%)	0.50	Intraoperative	Warming blanket
Respiratory Depression	SpO_2 < 92% or RR < 8	0 (0%)	0 (0%)		-	

M Group: Magnesium Sulfate + Bupivacaine; D Group: Dexmedetomidine + Bupivacaine. P values: chi-square or Fisher's exact test, as appropriate.

Discussion

In a post-hoc exploratory subgroup analysis of trauma patients (fracture fixation, n=40), the benefit of Dex was magnified: sensory block duration was 358 ± 50 min vs 265 ± 42 min (mean difference 93 minutes, $p<0.001$) and 24-h pethidine requirement was 78 ± 20 mg vs 135 ± 35 mg ($p=0.001$). While injury type seems to affect the outcome, this was not a planned analysis, so these findings are only suggestive and need confirmation in future studies.

Our findings show that dexmedetomidine provides better outcomes than magnesium sulfate for epidural anesthesia in orthopedic surgery. The much quicker sensory block onset (8.2 versus 12.4 minutes, $p<0.001$) fits the known pharmacodynamics of α-2 agonists, which improve nerve conduction blockade via hyperpolarization of nociceptive channels. The prolonged analgesia period (342 versus 278 minutes) is especially significant not only statistically but also clinically: the 64-minute difference with a 95% confidence interval of 47-81 minutes approaches the minimum clinically important difference (MCID) of 60 minutes reported by some investigators for postoperative pain control [13-14].

A unique exploratory and novel aspect of our study is the observation of potential sensory-motor dissociation. While onset times were similar, Group D showed a tendency toward longer duration (225 vs. 210 minutes, $p=0.12$), without reaching statistical significance. This pattern implies that dexmedetomidine may have a selective effect on sensory versus motor fibers, possibly using different modulation of Aδ and C fibers versus motor neurons [15].

However, we emphasize that this observation is exploratory and requires prospective validation in a study specifically powered to detect sensory-motor dissociation. No previous study comparing dexmedetomidine and magnesium sulfate in epidural anesthesia has reported this potential dissociation. If confirmed, this finding has potential clinical implications aimed at quick mobilization for quick recovery, where preservation of motor function is desirable.

The significantly earlier mobilization with dexmedetomidine, with a median of 8.5 hours compared with 11.2 hours ($p=0.02$), backs up its clinical relevance. The 2.7-hour reduction in time to first mobilization may translate into accelerated functional recovery and shorter hospital stays, though this hypothesis requires confirmation in dedicated studies.

Our findings support the investigation of epidural adjuvants by Shafi et al., whereby dexmedetomidine (versus magnesium sulfate) produced greater analgesia (307.3 ± 77.3 min), faster sensory block onset (13.1 ± 1.3 min), prolonged motor blockade, and mild sedation (scores >3) [8]. However, that study did not report on potential selective sensory-motor dissociation or trauma subgroup effects or functional outcomes, which we now add as novel exploratory observations.

Soundarya et al. revealed that the addition of Dex to Marcaine in a brachial plexus block causes an intensified onset of a sensory block and prolongation of a sensory and motor block. probably owing to its greater α_2-receptor affinity [16].

Though with significant differences, our results support earlier research on the neuraxial effects of dexmedetomidine. Our epidural findings extend this evidence to the neuraxial route. Onset Time: The 34% decrease in sensory onset we saw surpasses the 20–25% stated in lumbar plexus blocks [17].

This may indicate more epidural drug distribution owing to the vasoconstrictive characteristics of dexmedetomidine. Vasoconstriction brought on by dexmedetomidine lowers the systemic absorption of local

anesthetics, enabling higher concentrations to persist at the site of action, hence enhancing block effectiveness and shortening onset times [18].

Analgesia Duration: The clinically relevant important 64-minute prolongation observed in our orthopedic population exceeds the 40-50 minute extension observed in cesarean sections [19], which may be caused by synergistic effects with orthopedic surgical stress responses, suggesting that the magnitude of benefit may be procedure-dependent and particularly pronounced in orthopedic surgery. The restricted NMDA receptor involvement in epidural space pharmacology was indicated by the medium efficacy of $MgSO_4$ (278 minutes), which was shorter than some spinal anesthesia results [20].

The variable effects might involve: Several factors may explain our findings. Long-acting analgesia from dexmedetomidine could help early mobilization in patients undergoing joint replacement, an essential component of the early recovery process known as ERAS [21].

Opioid-Sparing Effect: In this population, the 29% decrease in 24-hour pethidine requirements (85 mg vs. 120 mg, p=0.003) may reduce postoperative nausea and vomiting risks.

In fracture patients (358 minutes of analgesia vs. 265 minutes in the $MgSO_4$ group), this point to a trauma subgroup benefit that has not been previously reported for this adjuvant comparison.

Several factors likely contribute to these differences: First, dexmedetomidine's dual spinal (α-2A) and supraspinal (locus coeruleus) actions vs. $MgSO_4$'s mainly presynaptic NMDA blockade [22]. Second, mild vasoconstriction by dexmedetomidine may delay systemic absorption, while $MgSO_4$'s vasodilation could accelerate clearance [15]. Third, dexmedetomidine may potentiate bupivacaine's sodium channel blockade through membrane stabilization [23]. Regarding the choice of magnesium sulfate as a comparator, we acknowledge that intravenous magnesium has demonstrated analgesic effects and may offer similar benefits without neuraxial administration. However, our study was designed to address a specific clinical question: in patients where the anesthesiologist has decided to use an epidural adjuvant, which of these two commonly used agents provides superior outcomes? Several recent randomized trials continue to use epidural magnesium sulfate as an intervention or comparator, supporting its ongoing clinical relevance. We suggest future studies directly compare epidural versus intravenous magnesium to further inform clinical decision-making.

The observed 8% incidence of bradycardia with dexmedetomidine, while clinically manageable, warrants cautious use in elderly patients or those with conduction abnormalities, and prolonged postoperative monitoring may be acceptable. Lower dosages (e.g., 3 μg) for a balance between efficacy and safety should be investigated in future research. Prophylactic administration of anticholinergic agents such as glycopyrrolate or atropine prior to dexmedetomidine administration could be considered as a practical strategy to reduce bradycardia risk, particularly in high-risk patients (e.g., those with baseline bradycardia, elderly patients, or those on beta-blockers). However, routine prophylactic use is not standard practice in our center due to potential side effects, and we reserved atropine for treatment of clinically significant bradycardia (HR < 45 bpm). Future studies should evaluate the risk-benefit profile of prophylactic anticholinergics in this context. We recognize that both dexmedetomidine and magnesium sulfate are used off-label for epidural administration. While no major neurotoxicity signal has been identified in available clinical studies, the uncertainty regarding long-term neuraxial safety deserves careful consideration. Preclinical studies have demonstrated no significant neurotoxicity at clinically used doses, but long-term follow-up studies are lacking. Clinicians using these agents should follow institutional protocols, obtain informed consent regarding off-label use, and adhere to recommended monitoring guidelines.

The effectiveness of dexmedetomidine as one of the epidural adjuvants in several meta-analyses has been confirmed [24], and others have shown benefits of magnesium sulfate [20]. However, because no trial has directly randomized these two agents against each other for lower limb orthopedic surgery under epidural anesthesia, with detailed block characterization and functional outcomes, previous guidelines and clinical decisions have relied on indirect comparisons. Our head-to-head design provides a higher level of evidence for choosing between these two available options.

The observed 64-minute sensory block advantage and the potential sensory-sparing profile suggest dexmedetomidine as a preferred adjuvant when prolonged pain relief without motor delay is desired, though prospective confirmation is needed.

Our post-hoc trauma subgroup analysis (n=40) revealed that fracture patients derived an even greater benefit from Dex: sensory block prolonged by 93 minutes (vs. 64 minutes overall) and pethidine consumption reduced by 57 mg (vs. 35 mg overall). To our knowledge, this is the first evidence suggesting that the comparative efficacy of these adjuvants may vary by surgical etiology (trauma versus elective arthroplasty). While exploratory, this finding opens a new research avenue into the injury-specific pharmacodynamics of neuraxial adjuvants.

Limitations

First, Single-Center Design: A multi-center verification would increase generalizability. Second, fixed adjuvant doses: An evaluation of the dose-response would help

determine the best regimens. Third, Long-Term Consequences: Follow-up beyond 24 hours would evaluate continuing advantages and long-term neurological safety. Fourth, the use of pethidine as a rescue analgesic, while standard in our center and many resource-limited settings, limits the international generalizability of our findings. Pethidine is no longer recommended as a first-line opioid in many countries due to concerns about neurotoxicity, serotonergic effects, and normeperidine accumulation with seizure risk. Future multi-center studies using morphine or fentanyl would enhance the applicability of results to broader clinical practice.. Fifth, the observed sensory-motor dissociation was an exploratory finding, as the study was not specifically powered for this endpoint; our data show an absence of evidence of a significant difference in motor block duration, not evidence of equivalence. Sixth, both agents were administered epidurally as off-label interventions; our results should be interpreted with awareness of regulatory considerations. Seventh, we did not include an intravenous magnesium comparator group; this omission limits our ability to comment on whether epidural magnesium offers advantages over systemic administration. Eighth, cost-effectiveness analysis was not performed. Future investigations should examine the following: First, low-dose dexmedetomidine and MgSO4 may possibly interact synergistically. Second, customized treatments for arthroplasty versus trauma are procedure-specific protocols. Third, the cost-benefit analysis of these adjuvants. Fourth, prospective validation of the potential selective sensory motor dissociation and the trauma subgroup effect. Fifth, a head-to-head comparison of epidural versus intravenous magnesium to clarify the optimal route of administration.

Conclusion

This head-to-head randomized trial specifically designed for lower limb orthopedic surgery with detailed characterization of block characteristics and functional outcomes demonstrates that dexmedetomidine provides a longer lasting sensory block, faster onset, superior postoperative analgesia, earlier mobilization, and reduced opioid (pethidine) consumption compared to magnesium sulfate as an adjuvant to epidural bupivacaine in lower limb orthopedic surgery. However, we acknowledge that the use of pethidine as the rescue analgesic limits the international generalizability of our findings. Future studies should use morphine or fentanyl, which are more widely recommended in international guidelines, to facilitate broader applicability.

Exploratory findings include a potential 64 minute sensory prolongation approaching the threshold considered clinically significant, a possible sensory sparing effect without significant motor block increase, and magnified benefits in trauma patients. However, its use is associated with a higher risk of bradycardia. These findings require prospective validation, particularly the sensory-motor dissociation and trauma subgroup effects.

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