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Original Article

Transforaminal lumbar epidural injection of dexmedetomidine versus magnesium sulfate combined with dexamethasone for lower limb radicular pain management: a randomized, clinical trial

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Background: Epidural steroid injections are frequently used to treat chronic radicular pain of a discogenic origin; however, their efficacy remains limited. Magnesium sulfate and dexmedetomidine are emerging adjuvants with the potential to enhance the effectiveness and prolong the therapeutic duration of steroid injections.

Methods: In this randomized, double-blind study, 90 patients with unilateral lower limb radiculopathy due to lumbar disc prolapse who did not respond to conservative treatment for 12 weeks were assigned to three groups. The control group received dexamethasone (4 mg), lidocaine 2% (40 mg), and saline. The magnesium group received magnesium sulfate (200 mg) with dexamethasone and lidocaine. The dexmedetomidine group received dexmedetomidine (50 mg), dexamethasone, lidocaine, and saline. Pain intensity was assessed using the visual analog scale at 1 week and 1, 3, and 6 months post-treatment. Secondary outcomes included the Modified Oswestry Disability Index (MODI), analgesic consumption, and procedure-related complications.

Results: Both magnesium and dexmedetomidine significantly reduced pain, disability, and analgesic consumption for up to 3 months. By 6 months, the magnesium group demonstrated significant improvement in pain scores and MODI and a decline in ibuprofen use compared to the control and dexmedetomidine groups.

Conclusions: Magnesium significantly reduced pain intensity, disability, and analgesic consumption over a 6-month observation period.

Keywords: Epidural injections; Intervertebral disc displacemen; Magnesium; Radiculopathy; Visual analog score.

INTRODUCTION

Lumbar radicular pain of discogenic origin is a ubiquitous issue affecting nearly 5% of the population [1]. Lumbar disc prolapse can compress lumbar spinal nerves, resulting in intense, stabbing pain that significantly impacts the quality of life and imposes a substantial burden on healthcare systems [2]. Fortunately, the clinical course of radicular pain is generally favorable, with approximately 80–90% of patients showing improvement within three months through various conservative modalities. These modalities include selective cyclooxygenase enzyme inhibitors, selective serotonin reuptake inhibitors, back braces, and muscle relaxants [3].

In refractory cases, minimally invasive fluoroscopically guided epidural steroid injections may provide short-term pain relief [4]. Transforaminal epidural injection (TFEI) is a selective, target-specific intervention that enables precise deposition of the injectate into the ventrolateral epidural sac, where nerve root compression occurs [5]. TFEI is supported by level I evidence and is strongly recommended in cases of non-operable lumbar disc herniation [6]. However, limitations to the use of epidural steroids have been identified, including modest efficacy, salt and water retention, and risk of spinal cord thrombosis secondary to inadvertent intravascular injection [7]. These limitations highlight the urgent need for novel adjuvants that can extend and enhance the therapeutic efficacy of epidural steroids.

Magnesium and dexmedetomidine have garnered attention in the field of chronic spinal pain management owing to their purported anti-neuropathic effects. Epidural magnesium can mitigate central sensitization induced by excessive peripheral nociceptive stimulation through noncompetitive antagonism of N-methyl-D-aspartate (NMDA) receptors. Magnesium can block calcium influx and prevent excessive and continuous neuronal depolarization [8]. Conversely, dexmedetomidine reduces inflammatory responses via dual pre- and post-synaptic alpha-2 agonistic actions [9].

The aim of the present study was to appraise the 6-month efficacy of adding magnesium or dexmedetomidine to epidural steroids for the treatment of radicular lower limb pain. This may significantly lead to an improved quality of life and alleviation of strain in the medical health system.

The primary objective of this study was to evaluate the therapeutic effects of transforaminal lumbar epidural magnesium sulfate and dexmedetomidine injections on pain intensity. Secondary outcomes included functional disability and analgesic consumption in patients with lower limb radiculopathy secondary to herniated lumbar discs.

MATERIALS AND METHODS

Study design and participants

This prospective randomized study adhered to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of the Faculty of Medicine at Fayoum University (approval number: R/219). The study was registered at ClinicalTrials.gov (NCT05271721). A total of 90 participants were enrolled, with recruitment beginning on March 1, 2022, and follow-up concluding in May 2023. This clinical trial was prospectively registered on February 26, 2022 and adherence to CONSORT guidelines was ensured.

The study included consenting adult patients of both sexes, aged 25 or older, who presented with clinical and lumbosacral magnetic resonance imaging evidence of lumbar disc herniation at one or two segments, accompanied by radicular pain consistent with the level of herniation. This radicular pain had been refractory to medical treatment and physiotherapy for at least 3 months. All candidates were classified as American Society of Anesthesiologists physical status grade I or II [10].

The primary outcome measure was pain intensity, evaluated using the visual analog scale (VAS) at one week, and at one, three, and six months post-procedure. The secondary outcomes included the Modified Oswestry Disability Index (MODI) and analgesic consumption at the same time points. Complications associated with this procedure were also documented. The exclusion criteria included isolated low axial pain without radiculopathy, diabetes, sacroiliitis, motor and/or neurological deficits, cauda equina syndrome, or reluctance to participate.

The enrolled participants were assigned to one of three groups. The first group received a transforaminal lumbar epidural injection of dexamethasone (4 mg/1 mL), lidocaine 2% (40 mg/2 mL), and sterile saline (1 mL) (30 participants; control group, C group). The second group received a transforaminal lumbar epidural injection of magnesium sulfate (200 mg/1 mL), dexamethasone (4 mg/1 mL), and lidocaine 2% (40 mg/2 mL) (30 participants; Magnesium group, MG group). The third group received dexmedetomidine (50 mg/0.5 mL), dexamethasone (4 mg/1 mL), lidocaine 2% (40 mg/2 mL), and 0.5 mL sterile saline (30 partic-

ipants; Dexmedetomidine group, DEX group). All patients were recruited from the Pain Clinic at Fayoum University Hospital. All patients were recruited from the Pain Clinic at Fayoum University Hospital.

Randomization and concealment

Randomization was performed using an opaque closed-envelope technique. An interventional therapist selected a sealed, unlabeled envelope containing a note that specified the assigned group. To ensure blinding, a non-interventional study member prepared the drugs according to a predetermined randomization sequence. The prepared drugs were then delivered to the therapist administering the injections in a sealed, tagged box and serially numbered in a specific alphanumeric order (e.g., 1A, 2A, 1B, and 2B). This serial number was recorded on the patient identification card to facilitate follow-up. The concealment key was securely locked and remained undisclosed until the end of the study.

All injections were administered by the same therapist to ensure consistency and minimize bias. Group assignments were concealed from both the outcome-assessing physician and patients to prevent bias. Prior to enrollment, all patients provided informed consent after receiving detailed explanations of the nature and objectives of the procedures. Additionally, the patients were thoroughly briefed on the study protocol and instructed on how to interpret the VAS for pain assessment, with 0 representing no pain and 10 representing the worst intolerable pain.

The patients familiarized themselves with the MODI, a validated questionnaire for assessing disability. The MODI consists of 10 items, each assigned a score from 0 to 5, with a maximum total score of 50. The total score was converted into a percentage, with higher percentages indicating a higher level of disability [11].

Therapeutic intervention

A pre-interventional evaluation, including both a clinical examination and radiological assessment, was conducted to ensure the accuracy of the injection site and its laterality. Prior to the procedure, a preliminary intravenous cannula (22 gauge) was inserted. Standard monitoring tools, including a 5-lead electrocardiogram, pulse oximeter, and non-invasive blood pressure cuff, were used. The patient was placed in the prone position with a pillow beneath the iliac crests to reduce lumbar lordosis.

Skin sterilization was achieved using 10% povidone-iodine, followed by the application of a sterile drape. Under intermittent fluoroscopic guidance, a 3.5-inch, 22-gauge spinal needle (Becton) was directed towards the neural foramen using a sub-pedicular approach. Skin anesthesia along the injection tract was achieved by administering 3 mL of 2% lidocaine (60 mg). The needle tip was visualized within the posterosuperior aspect of the neural foramen to ensure that it was distal to the feeding posterior spinal artery. An injection of 2 mL of radio-opaque dye (Omnipaque 300, Iohexol-containing iodine, GE Healthcare) was administered, allowing visualization of the nerve course without vascular uptake. Subsequently, an injectate was administered.

After the procedure, the patient was transferred to an intermediate care unit, where vital signs and postprocedural complaints were meticulously documented for 3 h. Hourly sensory and motor assessments were performed by the administering physician to detect signs of neural injury. Symptoms indicative of an epidural hematoma, such as new-onset motor blockade, severe back pain, or persistent anesthesia corresponding to specific myotomes and dermatomes, were closely monitored. These symptoms were considered red flags and warranted immediate lumbosacral magnetic resonance imaging. Each patient received only a single injection during the study period.

Statistical analysis

The collected data were analyzed using the SPSS software (version 20.0, SPSS Inc.). The Kruskal-Wallis test was used to assess non-parametric quantitative data across the three groups, followed by the Mann-Whitney *U* test for pairwise comparisons between each pair of groups. Friedman's test was used to evaluate non-parametric quantitative data at different time points within each group, and subsequent pairwise comparisons were performed using the Wilcoxon Signed-Rank test. To account for multiple comparisons and reduce the risk of Type I errors, a Bonferroni correction was applied to the P values. Statistical significance was set at $P < 0.05$.

Sample size

The sample size was determined using the PASS program (version 2011, NCSS, LLC) with an alpha error of 5% and a power of 80%. Based on the findings of Shrestha et al. [12],

who reported a 50% reduction in pain scores with transforaminal steroid injections at three months, we hypothesized that the addition of magnesium sulfate or dexmedetomidine could extend the duration of analgesia up to six months. A sample size of 85 participants was calculated. Ultimately, 90 participants were enrolled to account for potential dropouts. Data were entered into Excel and analyzed using IBM SPSS Statistics for Windows (version 25.0, SPSS Inc.).

RESULTS

A total of 105 participants were recruited, 15 of whom were excluded because they either declined to participate or required multiple injections (CONSORT, Fig. 1). The demographic and clinical data were comparable across the study groups (Table 1).

The pain scores, detailed in Fig. 2, demonstrated statistically significant differences between the pre- and post-treatment assessments at all follow-up intervals, except for the C and DEX groups at the 6-month mark (P = 0.624 and 0.51, respectively). Significant differences were observed in the intergroup comparisons between the C group and both MG and DEX groups at 1 week, 1 month, and 3 months post-procedure (P = 0.043, 0.032, 0.021 for the MG group and 0.04, 0.021, and 0.013 for the DEX group, respectively). At the 6-month follow-up, significant differences were noted between the MG group and the C and DEX groups (P = 0.003 and 0.03, respectively). Among the three groups, statistically significant differences were evident at all follow-up visits (P = 0.042, 0.011, 0.02, and 0.004, respectively).

Table 2 presents data on the MODI between the groups. Significant differences were noted between the C and MG groups at all follow-up visits (P = 0.04, 0.03, 0.01, and 0.003, respectively), as well as between the C and DEX groups at 1 week, 1 month, and 3 months post-intervention (P = 0.03, 0.04, and 0.02, respectively). Notably, a significant difference

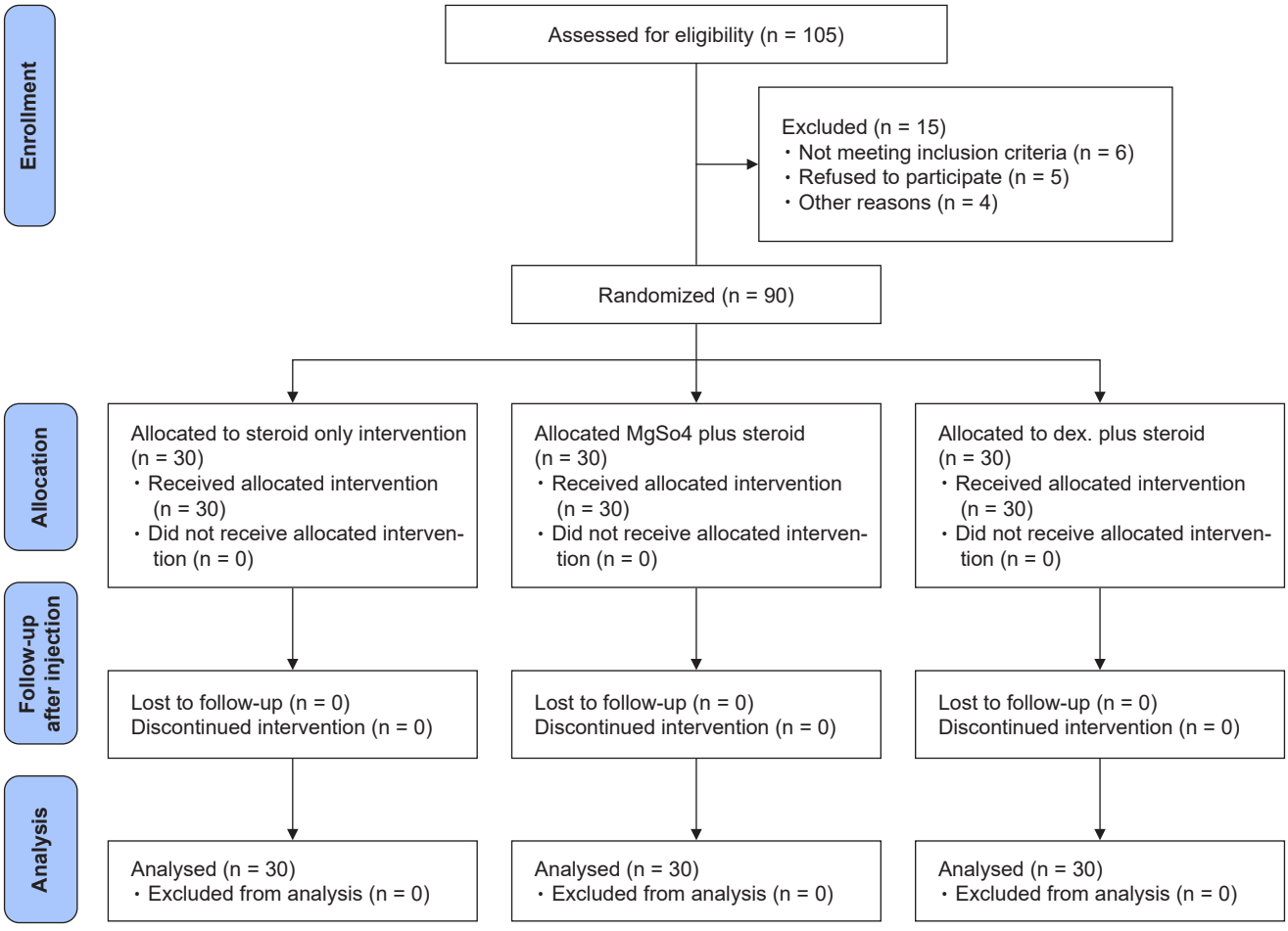

Fig. 1. CONSORT flow chart.

Table 1. Shows the Demographic and Clinical Data among the Studied Groups

Variable	Group C (N = 30)	Group MG (N = 30)	Group DEX (N = 30)
Age			
Range	25–69	34–64	47–75
Mean ± SD	50 ± 10	48 ± 7	45 ± 9
Sex			
M	14 (46.7)	12 (40.0)	17 (56.7)
F	16 (53.3)	18 (60.0)	13 (43.3)
BMI			
Range	27–34	25–36	28–33
Mean ± SD	29 ± 4	27 ± 3	25 ± 4
Level of prolapse			
L3–L4, L4–L5	6 (20.0)	8 (26.7)	9 (30.0)
L4–L5	8 (26.7)	10 (33.3)	7 (23.3)
L4–L5- L5–S1	5 (16.7)	8 (26.7)	9 (30.0)
L5–S1	11 (36.7)	4 (13.3)	

Values are presented as range (mean ± SD) or number (%). BMI: body mass index, C: control group, MG: magnesium, DEX: dexmedetomidine. Kruskal Wallis test for non- parametric quantitative data between the three groups followed by Mann Whitney *U* test between two groups. Friedman's test was used to analyze non-parametric quantitative data across different time points within each group. When significant differences were found, the Wilcoxon Signed-Rank test was applied to compare each pair of time points.

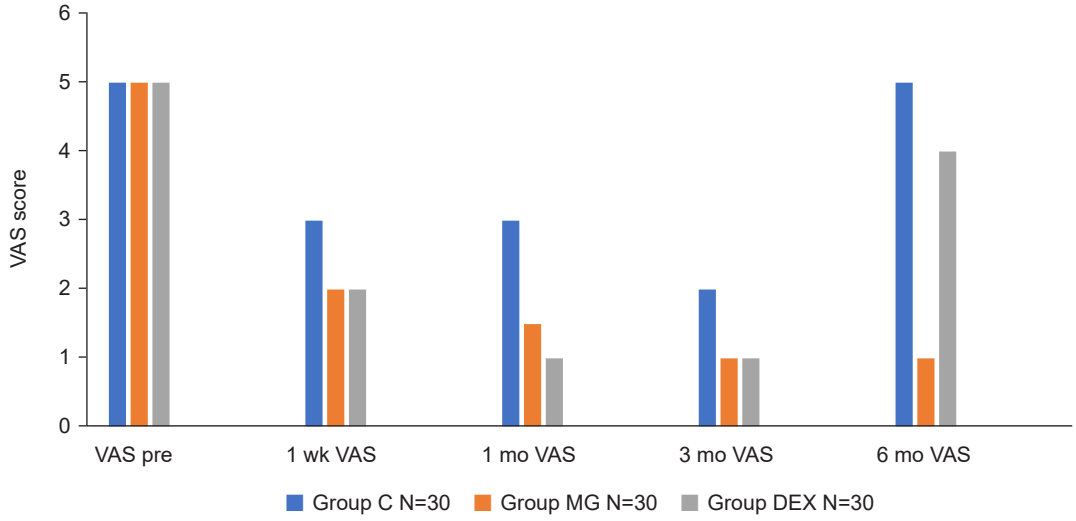

Fig. 2. Represents VAS values pre- and post-intervention among the studied groups. The pain scores, detailed in Fig. 2, demonstrated statistically significant differences between pre- and post-treatment assessments at all follow-up intervals, except for the C and DEX groups at the 6-month mark (P values = 0.6 and 0.5, respectively). Significant differences were observed in the intergroup comparisons between the C group and both the MG and DEX groups at 1 week, 1 month, and 3 months post-procedure (P = 0.04, 0.03, 0.02 for the MG group, and 0.04, 0.02, and 0.01 for the DEX group, respectively). At the 6-month follow-up, significant differences were noted between the MG group and the C and DEX groups (P = 0.003 and 0.03, respectively). Among the three groups, statistically significant differences were evident at all follow-up visits (P = 0.04, 0.01, 0.02, and 0.004, respectively). C: control, MG: magnesium, DEX: dexmedetomidine, VAS: visual analogue scale.

was observed between the DEX and MG groups at 6 months post-intervention (P = 0.02). Statistically significant differences were evident among the three groups at all follow-up visits (P = 0.04, 0.03, 0.01, and 0.01, respectively).

Significant differences in analgesic consumption were noted between the C group and MG group at all follow-up intervals (P = 0.03, 0.04, 0.003, and 0.001, respectively), and between the C and DEX groups at 1 week, 1 month, and 3 months post-intervention (P = 0.04, 0.04, and 0.03, respectively). A significant difference between the MG and DEX

Table 2. Presents Data on the Modified Oswestry Disability Index among the Studied Groups

Item	Group C (N = 30)	Group MG (N = 30)	Group DEX (N = 30)	C vs. MG	C vs. DEX	MG vs. DEX	Among 3 groups
Pre	60.5 (54.8, 69.3)	67.5 (58.8, 72.3)	66.5 (53.8, 71.5)	0.6	0.5	0.9	0.8
1 week	33 (20, 48)	12.5 (7, 15.3)	10 (8-, 16.3)	0.04*	0.03*	0.2	0.04*
1 month	36.5 (23.8, 48)	14 (10-, 19)	15 (10, 22)	0.03*	0.04*	0.4	0.03*
3 months	42 (37, 50)	14 (10, 18)	22 (19, 26)	0.01*	0.02*	0.5	0.01*
6 months	50 (47, 55)	16 (11.5, 22)	45 (38, 54)	0.003*	0.8	0.02*	0.01*

Values are presented as median (1Q, 3Q). C: control group, MG: magnesium, DEX: dexmedetomidine. Kruskal Wallis test for non-parametric quantitative data between the three groups followed by Mann Whitney *U* test between two groups. Friedman's test was used to analyze non-parametric quantitative data across different time points within each group. When significant differences were found, the Wilcoxon Signed-Rank test was applied to compare each pair of time points. *Significance at $P < 0.05$.

Table 3. Represents Data about Ibuprofen Consumption among the Studied Groups

	Group C (N = 30)	Group MG (N = 30)	Group DEX (N = 30)	C vs. MG	C vs. DEX	MG vs. DEX	Among 3 groups
Pre	1,800 (1,500, 2,000)	1,900 (1,700, 2,000)	1,800 (1,400, 2,200)	0.7	0.9	0.8	0.8
1 week	1,000 (750, 1,400)	400 (200, 600)	750 (650, 900)	0.03*	0.04*	0.9	0.04*
1 month	1,200 (800, 1,400)	400 (200, 600)	800 (600, 1,000)	0.04*	0.04*	0.549	0.03*
3 months	1,400 (1,000, 1,800)	600 (400, 1,000)	1,000 (800, 1,200)	0.003*	0.03*	0.539	0.01*
6 months	1,500 (1,200, 1,800)	800 (600, 1,000)	1,400 (1,200, 1,800)	0.001*	0.7	0.03*	0.01*

Values are presented as median (1Q, 3Q). C: control group, MG: magnesium, DEX: dexmedetomidine. Kruskal Wallis test for non-parametric quantitative data between the three groups followed by Mann Whitney test between two groups. Friedman's test was used to analyze non-parametric quantitative data across different time points within each group. When significant differences were found, the Wilcoxon Signed-Rank test was applied to compare each pair of time points. *Significance at $P < 0.05$.

groups was observed at 6 months post-procedure ($P = 0.03$), as shown in Table 3.

DISCUSSION

This study aimed to evaluate the long-term therapeutic benefits of fluoroscopically guided epidural injections supplemented with either magnesium sulfate or dexmedetomidine in individuals experiencing radicular lumbar pain. The incorporation of magnesium sulfate or dexmedetomidine resulted in a significant reduction in pain intensity, disability scores, and ibuprofen use for up to three months compared to the C group. Notably, these beneficial effects persisted beyond the immediate post-procedural phase, extending to the six-month follow-up exclusively in the MX group.

Prior to the implementation of these interventions, we thoroughly and rigorously investigated the safety and integrity of the neuro-axially administered pharmacological agents, ensuring this aspect was paramount. Nested meta-analyses have reported that epidural injection of either dexmedetomidine or magnesium sulfate is ethically sound and devoid of neurological concerns in both acute and chronic neuropathic pain management. Zhang et al. [13] conducted a meta-analysis and systemic review of eight clinical trials involving 846 participants to investigate the safety and validity of dexmedetomidine in epidural labor analgesia, using a dose of 0.5 μg/mL. They concluded that the combination of dexmedetomidine with local anesthetics improved the VAS scores, with no reported maternal or fetal complications, aside from transient maternal bradycardia. Imani et al. [14] compared the clinical impact of lumbar epidural injections of dexmedetomidine on chronic radicular low back pain. They provided comparisons between dexmedetomidine (50 μg) with ropivacaine (0.2%–4 mL) and triamcinolone (20 mg) with ropivacaine (0.2%–4 mL). Their findings demonstrated the superior efficacy of dexmedetomidine, as evidenced by significant reductions in pain and disability scores with no reported adverse neurological effects.

Magnesium has been extensively studied in various research settings and pain management clinics because of its purported anti-neuropathic properties. The efficacy of epidural magnesium in the treatment of radicular low back pain has garnered attention. Imani et al. [15] conducted a randomized clinical trial demonstrating that epidural magnesium injection (150 mg per single disc injection) was

more effective than 20 mg of triamcinolone in terms of long-term pain mitigation and disability improvement. The administered dose reached 300 mg in cases involving double lumbar disc injections, with no substantial neurological deficits. Furthermore, a systematic review encompassing data from 17 studies examined the efficacy of epidural magnesium administration in conjunction with local anesthetics in alleviating acute pain during elective surgeries in the adult population. Epidural magnesium doses ranged from 50 mg to 500 mg in different studies. This review indicated that magnesium extended the time until the first postoperative request for opioids without any actual or potential neural side effects [16].

An intriguing case report details the treatment of a 62-year-old woman with chronic postherpetic neuralgia localized to the left dorsomedial scapular region at the T3 vertebral level. The efficacy of a fluoroscopically guided epidural injection of magnesium (100 mg of magnesium sulfate combined with 1 mL of 0.2% ropivacaine for a total volume of 2 mL) was assessed. The procedure was repeated twice at one-week intervals (total dose of 300 mg). At the six-month follow-up, the patient reported being pain-free and discontinued all pain medications except for pregabalin [17].

Lumbar epidural injections are commonly used as minimally invasive therapeutic interventions with a surgical avoidance rate of 41%. However, their long-term effectiveness remains debatable. Benoist et al. [18] evaluated the effectiveness of epidural injections in alleviating radicular pain caused by herniated lumbar discs and concluded that these injections provided only short-term relief. Our study supports this finding, showing short-term improvements in the VAS and Modified Oswestry Disability Questionnaire scores lasting up to three months post-injection, with scores generally reverting to baseline by six months.

Magnesium plays a crucial role in neuroplasticity by reducing glutamate release and mitigating excessive calcium influx through its noncompetitive antagonistic action on NMDA receptors in a voltage-gated manner. This antinociceptive mechanism counteracts the central sensitization induced by persistent peripheral nociceptive stimulation. Additionally, magnesium deactivates reactive oxygen species, ameliorates secondary neuronal injury, and suppresses inflammation by attenuating the overproduction of pro-inflammatory cytokines such as interleukin-6 and substance P [19]. Consistent with our findings, a double-blind randomized trial recruited 80 patients with neuropathic low back pain and assigned them to two groups. The magnesium group received 1 g of MgSo4 in 250 mL saline 0.9% intravenously over 4 h every day for 2 weeks. Subsequently, oral magnesium was administered for four weeks (magnesium oxide 400 mg and magnesium gluconate 100 mg). The results revealed a significant decrease in pain severity and improved lumbosacral mobility at the six-month follow-up. A notable limitation was the lack of serum magnesium level measurements despite systemic administration [20].

Dexmedetomidine has garnered attention due to its selective alpha-2 agonistic properties in lumbar epidural injections. This mechanism involves decreasing norepinephrine release and enhancing the inhibitory effects of gamma-aminobutyric acid on ventrolateral preoptic neurons, thereby inhibiting central sensitization and attenuating wind-up [21]. Further evidence supports its efficacy in protecting against cellular damage caused by oxidative stress, inflammation, and hypoxia owing to its potent anti-inflammatory effects. Chen et al. [22] reported that dexmedetomidine inhibits the release of pro-inflammatory mediators, such as inducible nitric oxide and interleukin-16, thereby disrupting the inflammatory cascade.

Our findings align with those of Eskandr and Maseeh [23], who conducted a clinical trial involving two groups. The DEX group received 0.5 μg/kg of dexmedetomidine, 0.5 mg of bupivacaine, and 14 mg of betamethasone adjusted to a total volume of 20 mL with sterile saline, while the C group received 0.5 mg of bupivacaine plus 14 mg of betamethasone, also adjusted to 20 mL of sterile saline. Using an interlaminar epidural approach in patients with post-lumbar surgery syndrome, they reported a significant reduction in VAS scores up to 3 months post-intervention (median VAS score and range in the DEX group: 2–6, compared to 3–7 in the C group at 3 months; $P = 0.03$). Additionally, ibuprofen consumption was significantly lower in the DEX group (1,020 ± 260.66 mg) compared to the C group (1,290 ± 322.38 mg) at 3 months post-intervention, with a P value of 0.002. The Oswestry Disability Index showed significant improvement in the DEX group. Eskandr and Maseeh [23], attributed the observed reduction in pain scores to the anti-inflammatory action of dexmedetomidine. However, it is important to note that the pathology of failed back surgery syndrome differs from that of non-operated lumbar disc herniation, characterized by excessive fibrosis and dural tethering, which can twist the nerve roots beyond the herniated nucleus pulposus alone. Awad et al. [24] supported our findings by investigating the effects of adding preservative-free mag-

nesium (200 mg/1 mL) to lumbar epidural methylprednisolone (40 mg/1 mL) and bupivacaine 0.5% (10 mg/2 mL) in patients with lower limb radicular pain due to lumbar disc prolapse. They found that magnesium supplementation enhanced the efficacy of lumbar epidural injection for up to three months, leading to reductions in pain scores and functional disability. However, the primary limitation of this study is its relatively short follow-up period.

Consistent with our findings, Fathy et al. [25] conducted a randomized controlled trial involving patients with radicular low back pain. Patients received epidural injections of either magnesium sulfate (100 mg) plus 7 mg betamethasone and 1 mL lidocaine 2%, ozone (25 μg/mL) plus 7 mg betamethasone and 1 mL of lidocaine 2%, or 7 mg betamethasone and 1 mL lidocaine 2%. Pain severity and functional disability were assessed before the intervention, at 2 weeks, and at 1, 3, and 6 month post-intervention, along with measurement of anti-free radical enzymes (glutathione and superoxide dismutase). They reported that the administration of magnesium sulfate resulted in substantial long-term improvements, extending up to six months, in terms of both pain intensity and functional disability, and a significant increase in the scavenging enzymes in the magnesium and ozone groups 14 days post-injection. A limitation of our study was the relatively small dose of dexmedetomidine and the exclusion of patients with diabetes. Future research could extend the follow-up period to one year.

Epidural magnesium (200 mg) has been demonstrated to be safe and may potentiate and extend the therapeutic window of epidural injection for pain reduction and functional disability improvement for up to 6 months post-intervention. No serious procedure-related complications were reported, confirming the safety of dexmedetomidine and magnesium. Future studies should investigate various doses of epidural magnesium to evaluate their effects on pain alleviation and functional disability improvement over a one-year duration.

FUNDING

None.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Writing - original draft: Mina Maher Raouf, Fady Adib Abdel Malek, Tamer Youssef Elie Hamawy, Sadik Abdel-Maseeh Sadik, Mohammad Awad Elsaed. Writing - review & editing: Gehan Ibrahim Abdelrazek Salem. Data curation: Mina Maher Raouf. Formal analysis: Tamer Youssef Elie Hamawy. Methodology: Sadik Abdel-Maseeh Sadik. Project administration: Fady Adib Abdel Malek. Investigation: Mohammad Awad Elsaed. Software: Gehan Ibrahim Abdelrazek Salem. Supervision: Tamer Youssef Elie Hamawy.

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