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PLACENTAL EXTRACT AMELIORATES DEXAMETHASONE-INDUCED BEHAVIORAL ALTERATIONS IN PATIENTS WITH LUMBAR PAIN

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ABSTRACT

Dexamethasone (DEX) effectively relieves musculoskeletal pain but is frequently associated with insomnia and fatigue, while human placental extract (HPE) has been reported to reduce pain, fatigue, and sleep disturbance. This retrospective study examined whether co-administration of HPE could mitigate DEX-induced sleep disturbance and fatigue in 134 patients with chronic lumbar pain. Both DEX and HPE produced dose-dependent reductions in pain, and combined treatment enhanced analgesia beyond DEX alone. However, DEX alone worsened sleep quality with insomnia in three patients and did not improve fatigue. In contrast, HPE alone improved sleep and reduced fatigue below the clinical threshold, and these benefits were preserved in the combined DEX-HPE group. These findings suggest that co-administration of HPE mitigates DEX-induced sleep disturbance and fatigue while providing additive pain relief in patients with lumbar pain.

Keywords: Human Placental Extract; Dexamethasone; Pain; Sleep Disturbance; Fatigue

1 INTRODUCTION

Dexamethasone (DEX), a high-potency synthetic glucocorticoid, is widely used in the management of musculoskeletal pain owing to its rapid inhibition of the pain-aggravating cyclooxygenase and lipoxygenase pathways (1). Despite its therapeutic efficacy, however, DEX is associated with a range of adverse effects that can compromise patients' quality of life, among which insomnia and fatigue are prevalent and clinically significant.

In animal models, daily administration of 0.5 mg/kg DEX for 21 consecutive days has been shown to decrease the time spent in rapid eye movement (REM) sleep (2). In healthy human subjects, Moser *et al.* demonstrated that administration of 3 mg DEX every eight hours for 48 hours increased REM sleep latency and prolonged the percentage of time spent in arousal (3). Demisch *et al.* further reported that even a single 1 mg dose of DEX altered nocturnal melatonin production, a key regulator of the sleep–wake cycle (4). In a study of 100 children and adolescents with acute lymphoblastic

leukemia, Hinds *et al.* reported that DEX treatment induced disturbances in both sleep quality and fatigue (5). Mood disturbance has also frequently been observed during DEX treatment and often co-occurs with fatigue (6).

Given these concerns regarding DEX-induced alterations in sleep and fatigue, compensatory strategies to mitigate these adverse effects have been sought. Human placental extract (HPE), derived from human placenta, has been reported to exert anti-inflammatory, immunomodulatory, and restorative effects (7–9). HPE has been shown to reduce pain, fatigue, and sleep disturbance in several musculoskeletal diseases (10), and HPE-induced pain reduction has been closely associated with improvements in sleep quality and fatigue in these conditions (11).

In this retrospective study, we investigated the potential of HPE to prevent DEX-induced sleep disturbance and fatigue by co-administering HPE and DEX in patients with chronic lumbar pain.

2 MATERIAL AND METHODS

2.1 Subjects

This retrospective study included 134 patients with lumbar pain who presented to Cho Orthopaedic & Oriental Clinic in Seoul, South Korea, between May 2023 and December 2024. Patients ranged in age from 50 to 69 years and comprised 37 males and 97 females. Inclusion criteria were as follows: (1) widespread lower back pain with lower leg pain persisting for six months or longer, (2) normal findings on neurological examination, and (3) failure to achieve meaningful improvement with other complementary and alternative therapies. Exclusion criteria included known bleeding diathesis, autoimmune or inflammatory disease, diabetes mellitus, and use of non-steroidal anti-inflammatory drugs within four days prior to injection.

2.2 Placental Extract

Human placental extract (HPE), manufactured under the regulations of the Korean Food and Drug Administration (KFDA), was purchased from Green Cross Wellbeing Ltd. (Seoul, Korea). Briefly, human placentas were collected following full-term delivery and tested for human immunodeficiency virus and hepatitis B and C viruses. The placentas were then cut into pieces, defatted with acetone, and extracted with water through pepsin- and hydrochloric acid-catalyzed hydrolysis. The resulting extract was verified to be germ-free, anti-histaminic, and endotoxin-free in accordance with KFDA regulations. The final product was sterilized and packaged in 2 ml ampules approved for human injection. Insoluble macromolecules, including polysaccharides and polynucleotides, were excluded during the manufacturing process.

2.3 Therapeutic Interventions

All injections were administered using sterile 25-gauge, 40 mm needles. DEX was injected bilaterally into acupoint BL25 of the lower back, located 1.5 cun lateral to the lower border of the spinous process of the fourth lumbar vertebra (Fig. 1a). HPE was injected into acupoint CV6, located on the anterior median line of the lower abdomen, 1.5 cun below the umbilicus (Fig. 1b).

Patients were allocated to one of three treatment groups. The DEX-only group (n = 37) received 1.25–5 mg DEX at acupoint BL25 bilaterally, with half the dose administered to each side. The HPE-only group (n = 31) received 2–8 ml HPE at acupoint CV6. The combined DEX and HPE group (n = 66) received 2.5 mg DEX bilaterally at acupoint BL25 together with simultaneous administration of 2–8 ml HPE at acupoint CV6.

2.4 Data Collection and Analysis

Outcome measures were assessed before and after treatment. The primary outcome was pain intensity, assessed using the Visual Analogue Scale (VAS), on which 0 indicated no pain and 10 indicated the worst imaginable pain; patients marked their pain level on a 10 cm VAS before and after each treatment.

Secondary outcomes included sleep quality and fatigue severity. Sleep quality was assessed through structured patient interviews covering three domains: difficulty initiating sleep, total sleep duration, and refreshment upon wakening. Each domain was scored from 0 to 3, with higher scores indicating greater sleep disturbance. Fatigue was assessed using the nine-item Fatigue Severity Scale (FSS); the mean FSS score was calculated, with a score of ≥ 4.0 generally indicating clinically significant fatigue (12).

Data are presented as mean ± standard deviation. Differences before and after treatment within each group were analyzed using Student's paired t-test, with statistical significance set at $p < 0.01$.

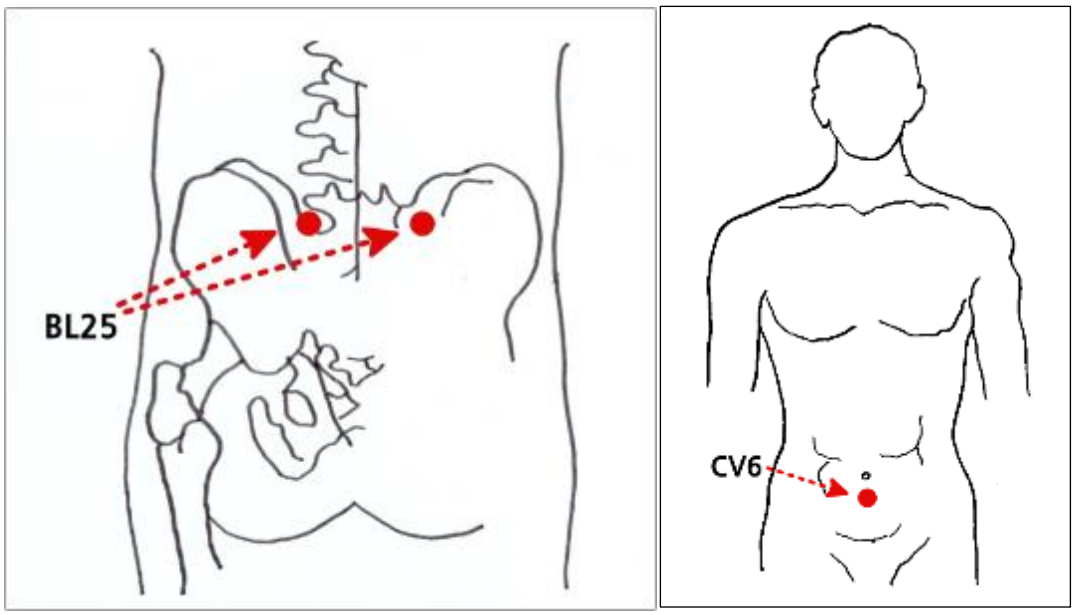
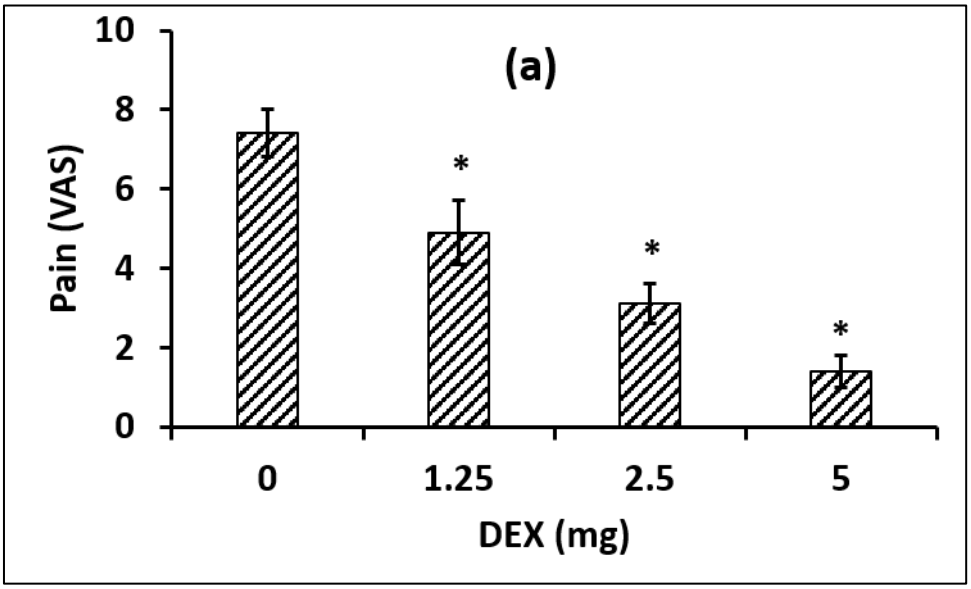


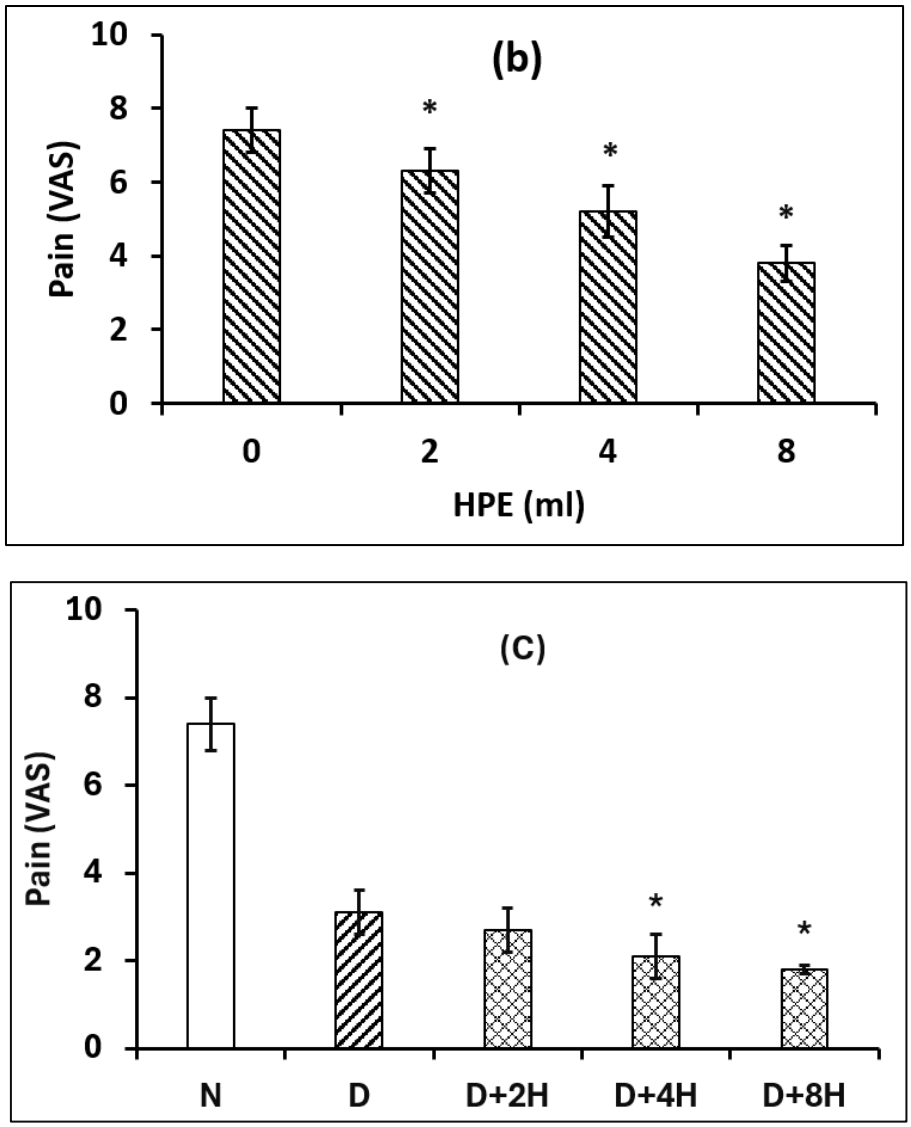
Figure 1: Loci of acupoints used in pharmacopuncture.

3 RESULTS

3.1 Pain Intensity

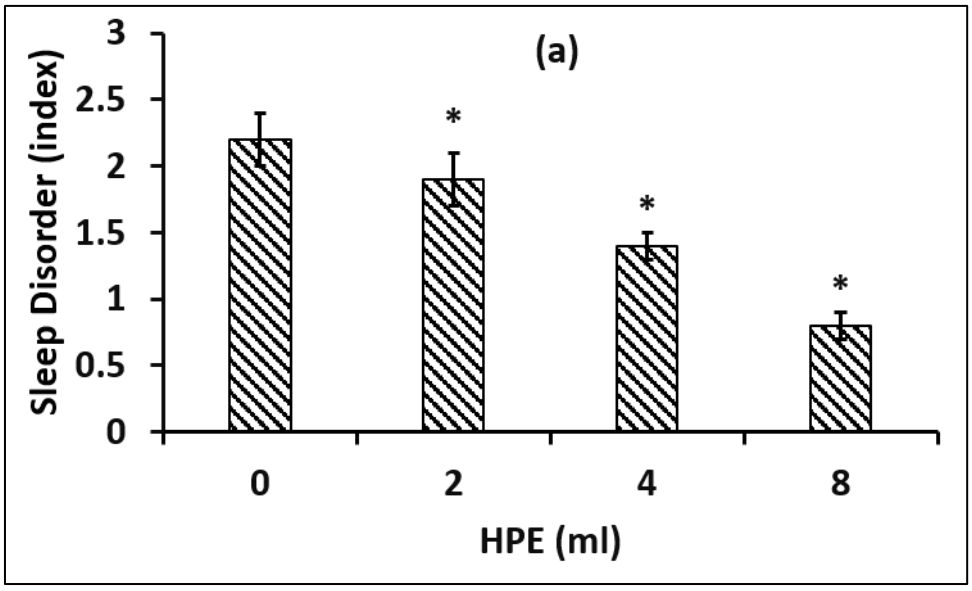
Before treatment, patients with lumbar pain reported a mean VAS score of 7.4, indicating severe pain. Both DEX and HPE produced substantial reductions in pain intensity: DEX demonstrated dose-dependent pain inhibition at doses ranging from 1.25 to 5 mg (Fig. 2a), and HPE reduced pain in proportion to volumes ranging from 2 to 8 ml (Fig. 2b). Notably, co-injection of HPE with 2.5 mg DEX produced a greater reduction in pain than 2.5 mg DEX alone (Fig. 2c), suggesting an additive analgesic effect of the combined regimen.

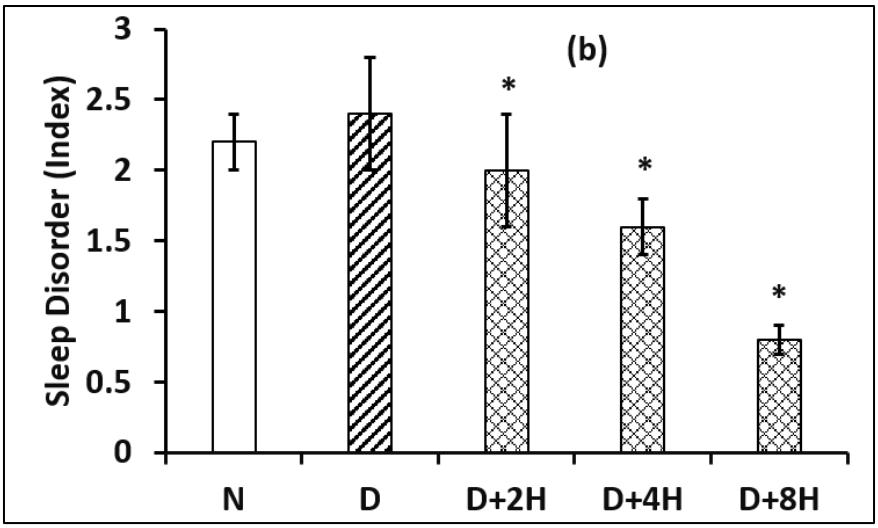




The Y-axis represents the degree of pain, expressed as VAS score. (a) DEX alone, (b) HPE alone, and (c) combined DEX and HPE. In (c), N represents the untreated (none) group; D represents the DEX-treated group (2.5 mg); and D+2H, D+4H, and D+8H represent groups treated with DEX (2.5 mg) combined with 2, 4, and 8 ml of HPE, respectively. *$p < 0.01$ vs. control (in a, b) or $p < 0.01$ vs. D (in c).

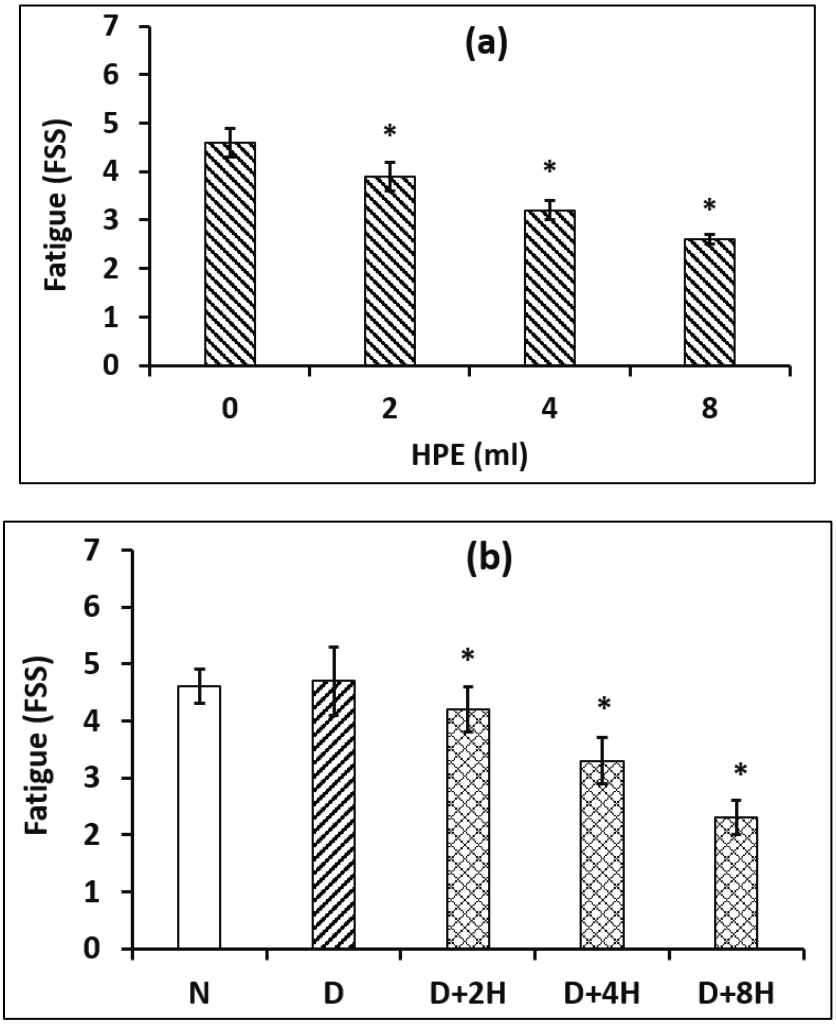
Figure 2: Effects of DEX, HPE, and Combined DEX and HPE Treatment on Pain.





The Y-axis represents the degree of sleep disorder. (a) HPE alone group, *p < 0.01 vs. control. (b) Combined DEX plus HPE group, *p < 0.01vs. D. In (b), N represents the untreated (none) group; D represents the DEX-treated group (2.5 mg); and D+2H, D+4H, and D+8H represent groups treated with DEX (2.5 mg) combined with 2, 4, and 8 ml of HPE, respectively.

Figure 3: Effects of DEX, HPE, and Combined DEX and HPE Treatment on Sleep Disorder.



The Y-axis represents the fatigue severity scale. (a) HPE alone group, *p < 0.01 vs. control. (b) Combined DEX plus HPE group, *p < 0.01 vs. D. In (b), N represents the untreated (none) group; D represents the DEX-treated group (2.5 mg); and D+2H, D+4H, and D+8H represent groups treated with DEX (2.5 mg) combined with 2, 4, and 8 ml of HPE, respectively.

Figure 4: Effects of DEX, HPE, and Combined DEX and HPE Treatment on Fatigue.

3.2 Sleep Quality

Treatment with 2.5 mg DEX alone caused a modest change in sleep patterns: after a single injection, three patients developed insomnia, and the sleep disorder index increased from 2.2 to 2.4 (Fig. 3b). In contrast, HPE alone improved sleep depth and next-morning vitality, reducing the sleep disorder index from 2.2 to 0.8 at the 8 ml HPE dose (Fig. 3a). In the combined DEX and HPE group, sleep initiation improved and nocturnal awakenings decreased compared with 2.5 mg DEX alone (Fig. 3). As HPE volumes of 2 to 8 ml were co-administered with 2.5 mg DEX, the sleep disturbance index decreased in proportion to the volume of HPE administered (Fig. 3b).

3.3 Fatigue Severity

Fatigue improvement was evident in the HPE-treated groups. The baseline FSS score of 4.6 indicated clinically significant fatigue, whereas HPE treatment reduced the FSS score to 2.6—below the clinical threshold—at the 8 ml HPE dose (Fig. 4a). In the DEX-only group, the FSS score was 4.7 after treatment (Fig. 4b). When 2–8 ml HPE was added to 2.5 mg DEX, the mean FSS score decreased to 2.6, indicating a meaningful improvement in fatigue with HPE co-administration (Fig. 4b).

4 DISCUSSION

Pharmacopuncture, a treatment modality that combines traditional acupuncture with the injection of pharmacological agents at specific acupoints, has gained increasing clinical attention as an integrative approach to pain management (13). DEX administered via pharmacopuncture at acupoint BL25 demonstrated favorable, dose-dependent outcomes in alleviating musculoskeletal pain.

However, a single injection of 2.5 mg DEX induced mild sleep disturbance and fatigue in patients. Co-administration of HPE alongside 2.5 mg DEX was associated with improvements in both disturbed sleep quality and fatigue.

Consistent with the insomnia findings, the DEX-only group showed increased fatigue severity after treatment, as reflected by higher FSS scores, likely attributable to DEX-induced sleep disturbance. In contrast, the HPE-only group showed a significant reduction in fatigue from baseline. The combined DEX and HPE group had significantly lower FSS scores than the DEX-only group, indicating that HPE co-administration effectively attenuated DEX-associated fatigue.

The mechanism by which HPE alleviates sleep disturbance and fatigue may be understood in the context of its established clinical benefits in menopausal women. Previous studies have reported that HPE administration in women experiencing menopause significantly reduces insomnia (14), and that this improvement in sleep quality subsequently leads to reduced fatigue (15). Several reports have described a relationship between estrogen and sleep modulation: estrogen replacement therapy has been shown to improve sleep quality, facilitate sleep onset, and reduce nocturnal restlessness and awakenings in postmenopausal women (16, 17). The beneficial effects of estradiol treatment on sleep quality have also been demonstrated in castrated male rats (18).

Notably, HPE contains estradiol and estradiol-related fragments, suggesting that its beneficial effects on sleep disturbance may be attributable, at least in part, to its estradiol component (15).

Taken together, these findings suggest that co-administration of HPE with DEX offers multifaceted therapeutic benefits in patients with musculoskeletal pain: DEX provides rapid and effective pain relief, while HPE concurrently ameliorates sleep disturbance and fatigue, which may further contribute to improved pain outcomes through restoration of normal sleep patterns.

This study has several limitations. Its retrospective design and relatively small sample size limit the generalizability of the findings, and the absence of a placebo-controlled arm and blinding may introduce bias. Future studies should employ a double-blind, randomized, placebo-controlled design, adequately powered for both fatigue and sleep outcomes, with a priori sample size calculation

5 CONCLUSION

Co-administration of human placental extract effectively mitigated dexamethasone-induced sleep disturbance and fatigue in our cohort of patients with lumbar pain.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of informed consent

The study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all the participants.

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