Observational Study

Pain Reduction and Changes in Serum Cortisol, Adrenocorticotropic Hormone, and Glucose Levels after Epidural Injections With Different Doses of Corticosteroid

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Background: An epidural steroid injection (ESI) effectively relieves acute lumbar discogenic radicular pain. Corticosteroids, a key ESI component, reduce pain by curbing inflammation and blocking pain signal transmission via C-fibers. While prior research confirms the efficacy of 40 mg and 80 mg methylprednisolone, the effectiveness of lower doses remains uncertain.

Objectives: This trial aimed to compare the pain-relieving effects of ESI using varying methylprednisolone doses (10 mg, 20 mg, and 40 mg). Additionally, it sought to examine changes in fasting plasma glucose (FPG), serum cortisol, and serum adrenocorticotropic hormone (ACTH) levels across these groups.

Study Design: A prospective observational study.

Setting: Department of Pain Medicine, Affiliated Jinling Hospital, Medical School of Nanjing University, People's Republic of China.

Methods: Ninety-three patients underwent a single epidural injection of methylprednisolone at different doses: 10 mg (n = 28), 20 mg (n = 32), and 40 mg (n = 33). We evaluated their Numeric Rating Scale (NRS-11) score and Oswestry Disability Index (ODI) score at preinjection and 7 days postinjection. We also measured FPG, serum cortisol, and ACTH levels at baseline and one day postinjection.

Results: Significant differences were observed in the likelihood of achieving substantial pain relief among the 3 groups at 7 days postinjection. Specifically, 10 mg vs 20 mg had an odds ratio (OR) of 6.546 (95% CI, 1.161 - 26.513, $P = 0.008$), and 10 mg vs 40 mg had an OR of 7.753 (95% CI, 1.98 - 30.353, $P = 0.003$). However, there was no significant difference between 40 mg and 20 mg, with an OR of 0.844 (95% CI, 0.239 - 2.987, $P = 0.793$) in Model 3. Additionally, the baseline NRS-11 score significantly predicted substantial pain relief, with an OR of 0.47 (95% CI, 0.287 - 0.768, $P = 0.003$). Furthermore, at 7 days postinjection, the ODI score was significantly lower in the 20 mg group ($P = 0.007$) and the 40 mg group ($P < 0.001$) compared to the 10 mg group. Moreover, the difference in serum cortisol and FPG between the 40 mg and 10 mg groups was more pronounced ($P < 0.01$), while the difference in ACTH was similar among all 3 groups ($P = 0.191$).

Limitations: Potential selection bias and a short follow-up period may have influenced our study, and certain imaging results were omitted from the regression models.

Conclusions: The effectiveness of ESI in relieving pain was found to be similar for both 20 mg and 40 mg doses, but with fewer changes in FPG and serum cortisol levels for the former (which were not statistically significant). As a result, it may be clinically viable to use a 20 mg dose for achieving short-term pain relief. Moreover, the baseline NRS-11 scores were found to be a reliable predictor of pain relief efficacy, with milder baseline pain intensity being associated with better pain relief outcomes.

Key words: Epidural steroids, epidural injection, herniated disc, methylprednisolone, dose, cortisol, glucose, adrenocorticotropic hormone

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Lumbar disc herniation is a localized or focal displacement of materials found in the intervertebral disc, comprising the nucleus pulposus, annulus fibrosus, and cartilage. This condition can trigger various symptoms and signs like low back pain, root radicular pain, weakness of the innervated area, and sensory disturbances (1,2). Sciatica is the most widespread type of root pain, with a prevalence rate ranging from 1.2% to 43%,with 90% of these cases resulting from disc herniation (3,4). Pain intensity is influenced by key factors such as inflammatory stimulation and mechanical compression (5).

Mysliwiec, et al (6) introduced the Michigan State University (MSU) Classification based on the location and size of lumbar disc herniation as seen on magnetic resonance imaging. They suggested that type 2-A lesions should be treated conservatively. Some researchers also recommend conservative treatment for sciatica in the first 6-8 weeks (4). Epidural steroid injection (ESI) is a conservative treatment strongly recommended by the American Society of Interventional Pain Physicians for lumbar disc herniation-associated pain treatment (Level I evidence) (7). Smith, et al (8) concluded that transforaminal ESI is effective for treating radicular pain caused by disc herniation.

Steroids reduce pain intensity by blocking prostaglandin synthesis and inhibiting the transmission of pain signals through C-fibers (9,10). Several studies have compared the analgesic efficacy and functional improvement of different doses of various steroids (11-16). Owlia, et al (14) compared the pain improvement of epidural injections of 40 mg and 80 mg of methylprednisolone. The Visual Analog Scale scores improved significantly from baseline, but remained similar between the 2 groups at 2 weeks, one month, and 3 months postinjection. Ozsoy-Unubol, et al (13) obtained similar results in their study. Although there was no significant difference between the 2 groups in their study, there was an improvement in pain, disability, and quality of life in both groups from baseline at 3 weeks and 3 months posttreatment. Currently, there are few ESI studies on the efficacy of doses lower than 40 mg of methylprednisolone. It is worth noting that ESI with steroids has a significant effect on blood glucose and the hypothalamus-pituitary-adrenal (HPA) cortex axis (17). The appropriate dose selection for clinicians often depends on the degree and duration of pain relief.

Our study aimed to examine pain reduction and functional improvement, alterations in fasting plasma glucose (FPG) and the HPA axis, and the potential adverse effects in patients suffering from acute discogenic radicular pain who undergo ESI treatment with 10 mg, 20 mg, and 40 mg of methylprednisolone. Additionally, we investigated the factors affecting significant pain relief post ESI with methylprednisolone.

Methods

Study Design

This study is a prospective observational trial. It was approved by the Clinical Trial Ethics Committee of the Jinling Hospital (2022-NZKY-007-01) and registered in the Chinese Clinical Trial Registry (ChiCTR2200066273). All patients signed informed consent forms.

Patients

Patients deemed eligible for inclusion in this study were those diagnosed with lumbar discogenic radicular pain, aged between 18 and 80 years, classified as MSU grade one or 2, and presenting with a Numeric Rating Scale (NRS-11) score of ≥ 4. Their pain must have persisted or worsened over a period of ≤ 4 weeks at the time of assessment, rendering them suitable candidates for epidural steroid injection (ESI) therapy.

Exclusions encompassed individuals with severe spinal deformities, nucleus pulposus prolapse or dissociation, a history of lumbar surgery, contraindications related to the puncture site, systemic or intraspinal infections, uncontrolled diabetes mellitus (DM), a prior history of hemorrhagic diseases, drug allergies pertinent to the treatment regimen, and a recent history of interventional therapy within 60 days preceding the study. Additionally, pregnant or lactating individuals and those with documented mental or psychological abnormalities were excluded. Patients who underwent other minimally invasive interventions during the follow-up period were also withdrawn from the trial.

Exposure Assessment

Patients were systematically numbered based on their inclusion time and underwent a comprehensive assessment. The injection level was determined by integrating imaging results with the patient's symptom presentation. Upon entering the treatment room, patients assumed a prone position with abdominal support from a cushion, while metal markers were meticulously positioned in the lumbar region. Patients were given precise instructions to remain still throughout the procedure. The transverse plane and the puncture

site were carefully identified following a localization scan via computed tomography.

Local infiltration anesthesia was administered at the designated puncture site using a 1% lidocaine solution. A 21G Touhy needle was employed for the puncture, directed through the parasagittal interlaminar approach. As per the pre-established trajectory, the needle was gently advanced in close proximity to the medial edge of the upper vertebra's inferior articular process. The needle's tip was then precisely positioned within the ventral epidural space. Verification of the needle tip's location within the epidural space was ascertained through the loss of resistance technique. Subsequent to confirming negative aspiration, patients received an injection of a 0.5 mL solution consisting of 0.75% ropivacaine blended with varying doses of methylprednisolone (total volume 3 mL).

Following ESI treatment, patients were categorized into groups based on the dose of methylprednisolone administered: 10 mg in Group A, 20 mg in Group B, and 40 mg in Group C.

Outcome Assessment

All patients were monitored for 7 days. The intensity of radicular pain was assessed on postinjection day 7 utilizing the NRS-11, which ranges from 0 to 10. Furthermore, the Oswestry Disability Index (ODI) was employed to gauge disability and impairment on the postinjection day 7. On the first day following the procedure, FPG, serum cortisol concentration, and serum adrenocorticotropic hormone (ACTH) concentration were systematically evaluated. FPG assessments were conducted at 6:00 AM, while cortisol and ACTH measurements were taken at 8:00 AM.

Throughout the entire follow-up period, any adverse effects were recorded. The primary outcome measure was significant pain relief observed on postinjection day 7, specifically defined as a reduction in the NRS-11 by ≥ 50% compared to baseline. Secondary outcomes were the ODI score on postinjection day 7, the variations in FPG, serum cortisol concentration, and ACTH concentration between baseline and the first day following ESI, as well as an assessment of any adverse effects. Patients who did not achieve significant pain relief on postinjection day 7 had the option to choose either reinjection or an alternative minimally invasive intervention.

Covariates

At the initial assessment, we gathered demographic information, health status, and conducted a comprehensive evaluation of each patient's condition. This included factors such as age, gender, height, weight, and the presence of hypertension and DM. We also recorded the medications employed for DM management. To prevent the inadvertent inclusion of patients with undisclosed DM, we performed measurements of FPG and hemoglobin A1C (HbA1C). Our criteria for diagnosing DM were as follows: in symptomatic patients, a diagnosis of DM was confirmed with an FPG level ≥ 7.0 mmol/L or an A1C criterion ≥ 6.5%. In cases where it was clear that hyperglycemia was absent, the presence of abnormal test results for FPG and A1C confirmed the diagnosis (18). The health status assessment of patients encompassed evaluating pain intensity and functional ability, which were quantified using the NRS-11 score and the ODI score, respectively.

Measurements of height and weight were conducted by nursing professionals upon admission; these values were utilized to calculate the Body Mass Index (BMI), calculated as kg/m^2. The lumbar magnetic resonance imaging results were evaluated by an experienced radiologist, who assessed the disc location, disc size, spinal canal stenosis, and foraminal stenosis. These imaging findings were subsequently converted into binary variables. Based on the MSU classification, the disc position was categorized as either intraspinal herniation (Zone-A, B, or AB) or nonintraspinal herniation (Zone-C). The size of the protrusion was classified as either Grade 1 or Grade 2. Spinal canal stenosis and foraminal stenosis were expressed as present or absent. A comprehensive visualization of the relationships among these variables can be found in Supplementary Fig. 1, which is depicted as a directed acyclic graph.

Sample Size

We computed the sample size using 2 distinct methods. In accordance with the pilot study, the NRS-11 scores on postinjection day 7 for each of the 3 groups were as follows: 3.8 ± 0.8 (Group A), 3.1 ± 1 (Group B), and 2.9 ± 1.1 (Group C). To detect a statistically significant difference among these groups, it was determined that 28 patients in each group would suffice, assuming a power (β) of 80% and a significance level (α error) of 0.05. Accounting for a dropout rate of 10%, the total sample size required was 93 patients.

Additionally, the anticipated rate of significant pain relief within 7 days was estimated to be approximately 65%. Given the study's design, which allowed for the inclusion of 5-11 independent variables in the logistic regression model, these calculations aligned

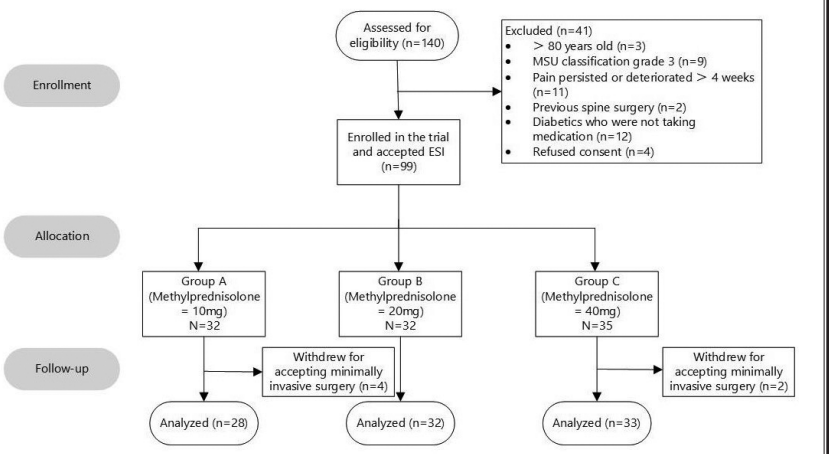

Fig. 1. *Flow chart of the study.*

with the study's requirements as specified in the directed acyclic graph.

Statistical Analysis

For statistical analyses, we utilized IBM SPSS Statistics 25.0 (IBM Corporation) and R Software 4.1.2, with the "foreign," "rms," and "ggplot2" packages. Statistical significance was defined as $P < 0.05$ with two-sided testing. Post hoc comparisons for significance levels were adjusted using Bonferroni correction. Continuous variables normality was evaluated using the Kolmogorov-Smirnov test. For those variables that exhibited a normal distribution, their descriptions were presented as means ± SD. Nonnormally distributed continuous variables were described using the median (interquartile range [IQR]). Categorical data were presented as frequency (percentage). To compare baseline characteristics among patients in different groups, we employed the one-way analysis of variance (ANOVA) test, Kruskal-Wallis test, or χ^2 test, depending on the nature and distribution of the data. All factors that demonstrated statistical significance were considered potential confounding variables.

We employed the Cochran-Armitage test to illustrate the trend of significant pain relief on postinjection day 7 using different corticosteroid doses. To delve into the specific relationship between these 2 variables, we established 3 multivariate binary logistic regression models. Given the uneven interval among the 3 doses, we established dummy variables with 10 mg as the reference group. Model 1 was adjusted for potential confounders, including age and BMI. Model 2 incorporated additional adjustments for imaging abnormalities, such as foraminal stenosis, spinal canal stenosis, the disc herniation size, and the disc herniation location. Building upon Model 2, Model 3 introduced further adjustments for variables like DM, baseline NRS-11 score, baseline ODI score, and baseline FPG. We employed the change-in-estimate method to select independent variables. Subsequently, we designated 40 mg as the control group and reconstructed the same 3 models.

To compare the differences among groups in terms of the ODI score on postinjection day 7, we utilized an analysis of covariance, wherein we adjusted for baseline ODI scores as covariates. For the differences in FPG, serum cortisol, and ACTH concentration between baseline and postinjection day one, we employed the Kruskal-Wallis test. Subgroup analyses were conducted based on the presence of DM. Since the lower limits of serum cortisol and ACTH concentration that could be tested are 10 ng/mL and 5 pg/mL, respectively, values falling below these thresholds were recorded as 10 ng/mL or 5 pg/mL for analysis. We compared the incidence of adverse effects using the χ^2 test.

To explore the interaction between the baseline NRS-11 and significant pain relief, we employed a multivariate binary logistic regression and assessed it on a continuous scale using restricted cubic spline curves. Subgroup analysis and restricted cubic spline curves are considered exploratory analyses. Missing data were primarily concentrated in the follow-up serum cortisol concentration and ACTH concentration. These missing data did not affect the analysis of the primary outcome. For secondary outcomes, we opted to delete cases with missing data instead of using imputation methods. The baseline values of serum cortisol and ACTH were missing for 7 cases, while the postoperative values of serum cortisol and ACTH were missing for 13 cases. In addition, the postoperative blood glucose values for one day were missing for 5 cases.

We performed 2 sensitivity analyses: 1) repeating all analyses by considering corticosteroid doses as ordinal variables, and 2) converting all quantitative variables into ordinal variables and then re-running all analyses.

Results

From January 2022 through October 2022, a total of 140 patients were assessed at the study's outset. During enrollment, 41 patients were excluded, leaving 99 patients who underwent ESI treatment. Six patients withdrew from the study to pursue alternative minimally invasive procedures during the 7-day follow-up period. Ultimately, 93 patients were included in the analysis, with 28, 32, and 33 individuals allocated to the 3 groups (Fig. 1). Among these patients, 45 (48.4%) were women and 48 (51.6%) were men, with a median age of 54 years (IQR, 28.5 - 67 years). The mean BMI was 24.36 ± 4.11. Notably, there was an imbalance in age (P = 0.034) and gender (P = 0.018) distribution, which were considered potential confounding factors (Table 1).

Table 1. *Demographic data, imaging results, baseline NRS-11 and ODI scores.*

	Overall (n = 93)	Group A (n = 28)	Group B (n = 32)	Group C (n = 33)	*P* Value
Age (years)	54 (28.5 - 67)	58 (43.5 - 71.75)	40 (23 - 58.5)	57 (35.5 - 67)	0.034
18 - 30	24 (25.8%)	5 (17.9%)	13 (40.6%)	6 (18.2%)	
31 - 40	8 (8.6%)	1 (3.6%)	3 (9.4%)	4 (12.1%)	
41 - 50	12 (12.9%)	4 (14.3%)	5 (15.6%)	3 (9.1%)	
51 - 60	19 (20.4%)	5 (17.9%)	4 (12.5%)	10 (30.3%)	
61 - 70	14 (15.1%)	6 (21.4%)	3 (9.4%)	5 (15.2%)	
71 - 80	16 (17.2%)	7 (25%)	4 (12.5%)	5 (15.2%)	
BMI (kg/m^2)	24.36 (± 4.11)	23.74 (± 3.8)	24.95 (± 4.97)	24.3 (± 3.42)	0.524
Gender					0.018
Women	45 (48.4%)	17 (60.7%)	9 (28.1%)	19 (57.6%)	
Men	48 (51.6%)	11 (39.3%)	23 (71.9%)	14 (42.4%)	
Diabetes Mellitus					0.129
Yes	40 (43%)	16 (57.1%)	10 (31.3%)	14 (42.4%)	
No	53 (57%)	12 (42.9%)	22 (68.7%)	19 (57.6%)	
Injection level					0.52
L3/L4	4 (4.3%)	2 (7.1%)	0 (0%)	2 (6.1%)	
L4/L5	49 (52.7%)	16 (57.1%)	18 (56.3%)	15 (45.5%)	
L5/S1	40 (43%)	10 (35.7%)	14 (43.8%)	16 (48.5%)	
Spinal canal stenosis					0.094
Yes	54 (58.1%)	21 (75%)	16 (50%)	17 (51.5%)	
No	39 (41.9%)	7 (25%)	16 (50%)	16 (48.5%)	
Foraminal stenosis					0.094
Yes	15 (16.1%)	8 (28.6%)	4 (12.5%)	3 (9.1%)	
No	78 (83.9%)	20 (71.4%)	28 (87.5%)	30 (90.9%)	
Herniation size					0.916
Grade 1	48 (51.6%)	14 (50%)	16 (50%)	18 (54.5%)	
Grade 2	45 (48.4%)	14 (50%)	16 (50%)	15 (45.5%)	
Disc location					0.816
Intraspinal	76 (81.7%)	22 (78.6%)	26 (81.3%)	28 (84.8%)	
Extraspinal	17 (18.3%)	6 (21.4%)	6 (18.8%)	5 (15.2%)	
Baseline ODI	49.74 (± 6.52)	51.14 (± 7)	48.56 (± 6.16)	49.7 (± 6.39)	0.313
Baseline NRS-11	6.37 (± 1.25)	6.61 (± 1.29)	6.5 (± 1.19)	6.03 (± 1.24)	0.15
Baseline FPG (mmol/L)	5.1 (4.8 - 5.7)	5.1 (4.8 - 5.775)	5.1 (4.7 - 6.25)	5.1 (4.8 - 5.55)	0.874

Normally distributed continuous variables were described as means (± SDs). And median (interquartile range [IQR]) was used to describe the nonnormally distributed continuous variables. Categorical data were reported as frequency (percentage). $P < 0.05$ is considered significant.
BMI: Body mass index (kg/m^2); NRS-11: Numeric rating Scale; ODI: Oswestry Disability Index; FPG: fasting plasma glucose.

Primary Outcome

Significant pain relief on postinjection day 7 was observed in 10 patients (35.7%) in Group A, 21 patients (65.6%) in Group B, and 26 patients (78.8%) in Group C. Initially, the Cochran-Armitage test (P < 0.001) demonstrated a linear correlation between corticosteroid doses and significant pain relief on postinjection day 7. Subsequently, we established 3 binomial logistic regression models to elucidate this relationship.

In Model 1, adjusting for age, BMI, and gender, a comparison of 10 mg versus 20 mg (odds ratio [OR] 3.381; 95% CI, 1.063 - 10.755; P = 0.039) and 10 mg versus 40 mg (OR 6.765; 95% CI, 2.127 - 21.51; P = 0.001) showed significant associations with significant pain relief, while the comparison of 40 mg versus 20 mg (OR 0.5; 95% CI, 0.155 - 1.609; P = 0.245) displayed a weaker correlation.

Model 2 indicated no significant change in the effect size of the 3 factors. Finally, in Model 3, after adjusting for the remaining covariates and using the change-in-estimate method to select 5 adjustments (spinal canal stenosis, herniation size, baseline NRS-11, baseline FPG, and DM), 10 mg versus 20 mg (OR 6.546; 95% CI, 1.161 - 26.513; P = 0.008) and 10 mg versus 40 mg (OR 7.753; 95% CI, 1.98 - 30.353; P = 0.003) consistently emerged as independent risk factors. However, the analgesic efficacy between 40 mg and 20 mg (OR 0.844; 95% CI, 0.239 – 2.987; P = 0.793) showed no significant difference (Table 2). Besides the baseline NRS-11 (OR 0.47; 95% CI, 0.287 - 0.768; P = 0.003), no other adjustments had P values below 0.05. Among the imaging-related factors, spinal canal stenosis (OR 1.707; 95% CI, 0.571 - 5.103; P = 0.339) and herniation size (OR 2.381; 95% CI, 0.829 - 6.833; P = 0.107) did not demonstrate significant associations with significant pain relief.

Secondary Outcomes

Following the ESI treatment, a comparison with Group A revealed that on postinjection day 7, ODI scores were smaller in Group B (P = 0.007) and group C (P < 0.001) (Table 3). Box plots illustrate that the difference in serum cortisol levels between Group C (median 90.75, IQR 41.625 - 138.224) ng/mL and Group A (median 20.5, IQR 8.35 - 105.3) ng/mL was significant (P = 0.007). However, no significant difference was observed between Groups A and B (median 55, IQR 37.75 - 95.075) ng/mL (P = 0.196), or between Groups B and C (P = 0.615). Differences in FPG were notable, with Group C (median 1.25, IQR 0.65 - 2) mmol/L having higher levels than Group A (median 0.25, IQR -0.175 - 0.975) mmol/L (P = 0.002). The differences between Groups A and B (median 0.85, IQR 0.125 - 1.475) mmol/L (P = 0.282), as well as between Groups B and C (P = 0.169), were not statistically significant. Conversely, differences in serum ACTH showed no significant variation among the 3 groups (P = 0.191) (Fig. 2).

Sensitivity and Exploratory Analyses

In the exploratory analyses, we divided our investigation into 2 sections. Initially, we scrutinized the relationship between baseline NRS-11 and significant pain relief, constructing 2 models (Fig. 3). The outcomes revealed that baseline NRS-11 was a substantial predictor for significant pain relief. We also identified a linear and negative association between baseline NRS-11 and the risk of incident significant pain relief using a restricted cubic spline regression with 3 knots (P nonlinear = 0.734) (Fig. 4).

In the subgroup analysis for patients without DM, Group C (median 84.1, IQR 31.725 - 129.35) ng/mL exhibited a more significant change in serum cortisol compared to Group A (median 18, IQR 2.5 - 38.2) ng/mL (P = 0.014). Furthermore, Group C displayed higher

Table 2. *Odds of obtaining ≥ 50% pain reduction at postinjection 7 days in different doses of methylprednisolone.*

	Adjusted Odds Ratio (95%CI)		
	Model 1	Model 2	Model 3
10 mg vs 20 mg	3.381 (1.063 - 10.755) *	4.264 (1.212 - 14.999) *	6.546 (1.616 - 26.514) **
10 mg vs 40 mg	6.765 (2.127 - 21.51) **	8.459 (2.352 - 30.423) **	7.753 (1.98 - 30.353) **
40 mg vs 20 mg	0.5 (0.155 - 1.609)	0.504 (0.147 - 1.732)	0.844 (0.239 - 2.987)

10 mg: methylprednisolone 10 mg (Group A); 20 mg: methylprednisolone 20 mg (Group B)
40 mg: Methylprednisolone 40 mg (Group C); *: P < 0.05; **: P < 0.01
Model 1: Adjusted for age, body mass index, and gender
Model 2: Adjusted for age, body mass index, gender, spinal canal stenosis, foraminal stenosis, herniation size, and disc location
Model 3: Adjusted for spinal canal stenosis, herniation size, baseline Numeric Rating Scale score, baseline fasting plasma glucose, and diabetes mellitus.

cortisol levels than Group B (median 55, IQR 36.8 - 129) ng/mL (P = 0.022). Differences in FPG were also notable among patients without DM, with Group C (median 1.25, IQR 0.125 - 1.875) mmol/L showing a greater increase than Group A (median 0.2, IQR -0.4 - 0.6) mmol/L (P = 0.022) (Fig. 5).

Our primary analysis results remained consistent across various sensitivity analyses, as detailed in Supplementary Table 1 and Supplementary Table 2.

Safety Analyses

The incidence of adverse effects in Groups A, B, and C was 7.1%, 15.6%, and 9% respectively, with no significant difference observed among the groups (P = 0.531). One patient who experienced a dural sac puncture reported dizziness and a headache after treatment (Table 4). Fortunately, there were no serious adverse effects such as epidural hematoma, epidural abscess, or steroid embolism in any of the 3 groups.

Discussion

In this observational study, we discovered that lumbar ESI administered with varying small doses of methylprednisolone resulted in varying degrees of pain reduction on postinjection day 7. In comparison to the 10mg dose, the 20mg and 40mg doses yielded a higher significant pain relief rate. Patients in the other 2 groups exhibited greater functional recovery than those in the 10 mg group. Furthermore, the efficacy of ESI is dependent on the baseline pain intensity, indicating that a lower baseline NRS-11 predicts better pain relief.

The ESI puncture approach comprises 3 methods: transforaminal (TF), interlaminar (IL), and caudal. Among these, TF and IL are widely used in clinical practice, with the former being the preferred approach. TF injection has a wider diffusion range into the ventral epidural space where lumbar disc herniation often occurs due to the thin posterior longitudinal ligament. However, at the cervical level spinal foramen, there exist radiculomedullary arteries, the vertebral artery, and anastomotic branches (19); while the lumbar spinal foramen may have the Artery of Adamkiewicz (20). The TF approach carries a high risk of accidentally puncturing the arteries, potentially leading to ischemic complications, especially when using particulate steroids (19,21). Our trial used the parasagittal IL approach to not only avoid severe accidents but also to achieve comparable anterior spread percentages and shorter fluoroscopy exposure time than the TF approach (22).

Previous trials that compared different doses of methylprednisolone mainly focused on 40 mg and 80 mg; they concluded that there was no significant difference in pain levels after injection between the 2 doses (13,14). However, a randomized double-blind controlled trial by Kang et al (12) enrolled 160 patients who received 2 TFESI of either 5 mg, 10 mg, 20 mg, or 40 mg of triamcinolone. They found that the number of patients achieving pain relief in the 5 mg group was

Table 3. *Data comparing ODI scores at 7 days postinjection.*

	Difference Mean (± SD)¶	Least mean difference (95% CI)	*P* Value♮
Group A	17.214 (± 5.769)	3.635 (0.823 - 6.448) §	0.007§
Group B	20.125 (± 4.125)	1.738 (-0.931 - 4.408) #	0.347#
Group C	22.182 (± 4.312)	5.374 (2.605 - 8.142) &	< 0.001&

Group A: Methylprednisolone 10 mg; Group B: Methylprednisolone 20 mg
Group C: Methylprednisolone 40 mg; §: Group A compared with Group B
#: Group B compared with Group C; &: Group C compared with Group A
♮: *P* values of comparisons were adjusted by Bonferroni correction
¶: ODI score 7 days postinjection minus baseline ODI score
ODI: Oswestry Disability Index

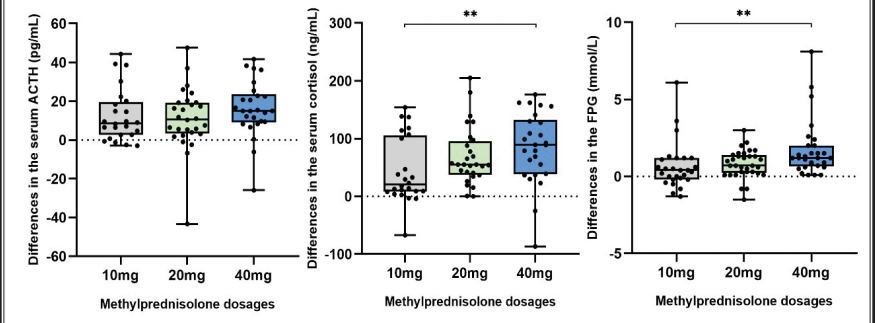

Fig. 2. *Box plots of differences in fasting plasma glucose (FPG), serum cortisol concentration, and serum adrenocorticotropic hormone (ACTH) concentration from baseline to one day postinjection compared among the 3 groups.*
10 mg: methylprednisolone 10 mg (group A); 20 mg: methylprednisolone 20 mg (group B); 40 mg: methylprednisolone 40 mg (group C); **: $P < 0.01$, all the P values of post hoc comparisons were adjusted by Bonferroni correction.

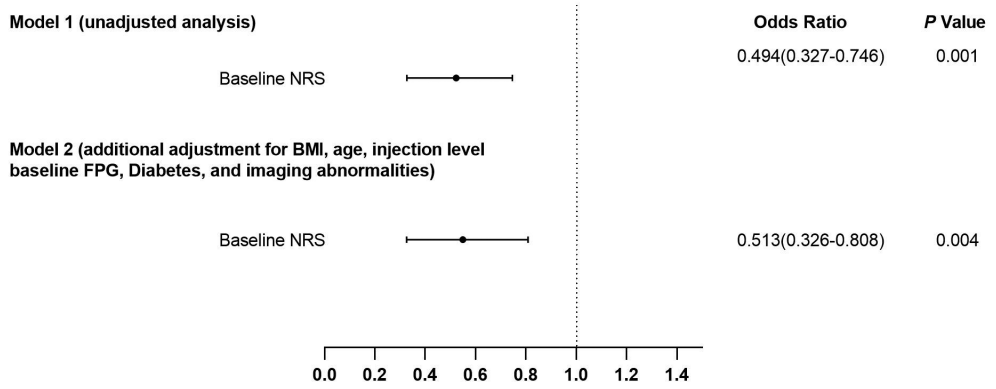

Fig. 3. *The correlation between baseline NRS-11 and significant pain relief (NRS-11 score decrease ≥ 50%) at 7 days postinjection.*
Model 1: Only included the baseline NRS-11 to construct univariate regression.
Model 2: Excluded 2 mediating variables (baseline ODI, and steroid dose), and adjusted for the rest of the 9 variables according to a directed acyclic graph.
FPG: fasting plasma glucose; BMI: body mass index; NRS-11: Numeric Rating Scale. Imaging abnormalities: spinal canal stenosis, foraminal stenosis, herniation size, and disc location.

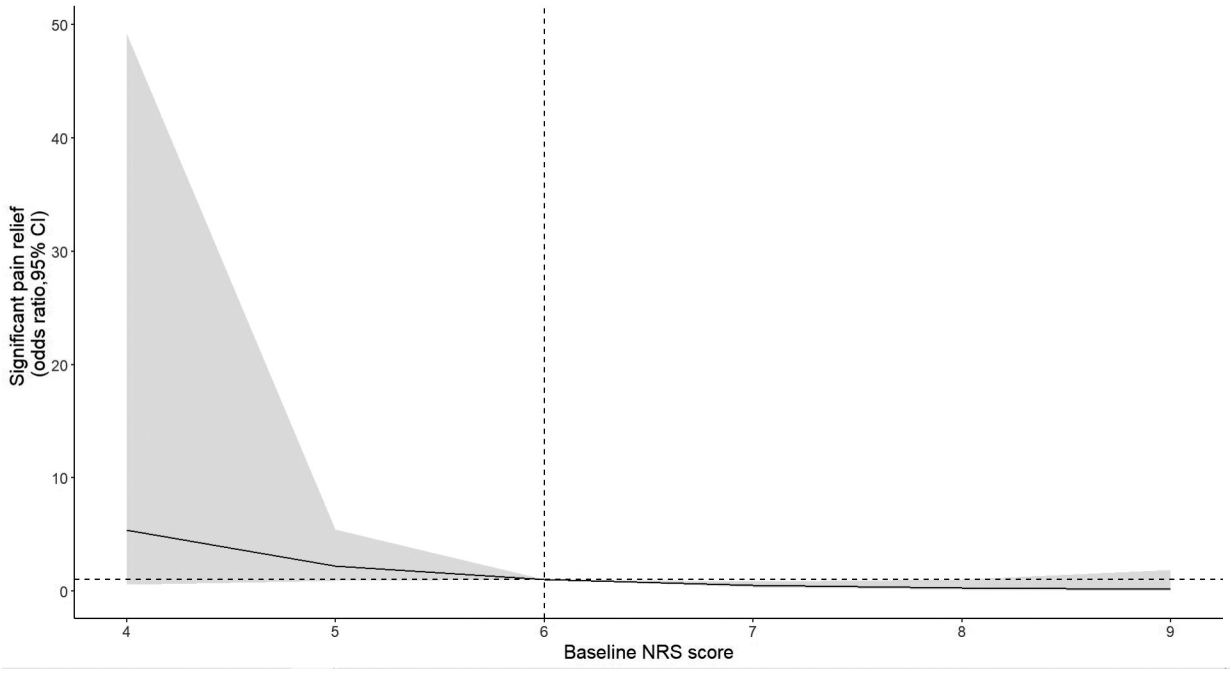

Fig. 4. *Association between baseline Numeric Rating Scale (NRS-11) score and significant pain relief (NRS-11 score decrease ≥ 50%) at 7 days postinjection using a restricted cubic spline regression model.*
Results were adjusted for body mass index, age, injection level, baseline fasting plasma glucose, diabetes mellitus, spinal canal stenosis, foraminal stenosis, herniation size, and disc location (Model 2). Restricted cubic spline regression model was conducted with 3 knots at the baseline NRS-11 was 4, 6, and 9. The shade represent the 95% CIs for the spline model. The dotted line parallel to the X-axis intersects the Y-axis, representing an odds ratio value of 1. The intersection of the dotted line parallel to the Y-axis and the X-axis represents the value of baseline NRS-11 when odds ratio is 1.
NRS-11: Numeric Rating Scale

significantly lower than in the other groups, and that verbal NRS-11 scores were higher than in the other groups one week after the first TFESI (12). This study looked at smaller doses of triamcinolone and found that the effectiveness of 20 mg and 40 mg is similar, but better than 10 mg (12). This result indicates a correlation between steroid doses and pain relief, which is not a simple positive linear association.

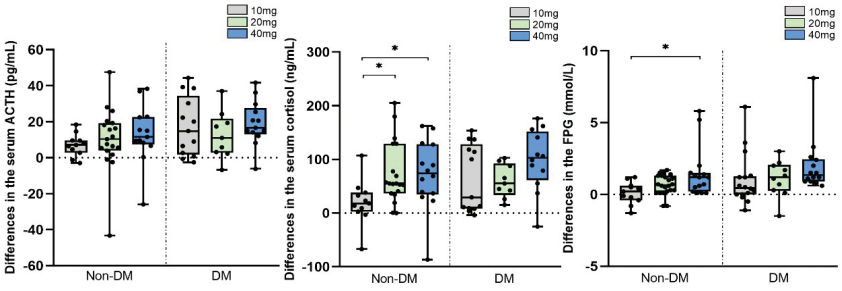

Fig. 5. *The subgroup analysis of differences in fasting plasma glucose, serum cortisol concentration, and serum adrenocorticotropic hormone concentration from baseline to one-day postinjection compared among the 3 groups.*
10 mg: methylprednisolone 10 mg (Group A); 20 mg: methylprednisolone 20 mg (Group B); 40 mg: methylprednisolone 40 mg (group C); *: $P < 0.05$, all the P values of post hoc comparisons were adjusted by Bonferroni correction.

As the dose increases to a certain point, the effects tend to become stable. Tagowski, et al (23) conducted a retrospective observational study comparing pain relief after ESI with triamcinolone or dexamethasone. They constructed 2 cohorts based on the type of steroids and found that the baseline NRS-11 score is an independent predictor of the chance for ≥ 50% pain relief at 4 weeks postinjection in the dexamethasone cohort (OR 0.86; 95% CI, 0.76 - 0.98; $P = 0.023$). Generalized additive models were used to analyze the nonlinear correlations, showing that there were fewer chances for ≥ 50% pain relief with increases in the baseline NRS-11 score from 3 to 7. Our study also found that the baseline NRS-11 score was an independent inhibiting factor (OR 0.514; 95% CI, 0.327 - 0.808, $P = 0.004$), but there was no plateau effect for high pain levels and the correlation was purely linear.

In our study, the change-in-estimate method was used to select 5 adjustments in Model 3, which could change the effect size of different steroid doses by more than 10%. However, the 95% CI of the OR in these adjustments all included one. This may indicate that the effect of those adjustments remains unstable among different individuals.

Lumbar spinal canal stenosis is a degenerative disease that worsens with age. The causes of spinal canal stenosis include disc herniation, facet joint hypertrophy, ligamentum flavum hypertrophy, and spondylolisthesis, all which can contribute to the displacement of nerve roots and cause radicular pain (24). Existing studies have reached inconsistent conclusions on the effect of spinal stenosis and its severity on pain relief post-ESI. Kim, et al (25) reviewed the records of patients who received ESI treatment for spinal canal stenosis and found that patients in the moderate group had lower NRS-11 scores than those in the severe group at 2 weeks postinjection. However, a secondary analysis by Turner, et al (26) found that spinal stenosis severity is not a consistent predictor of benefit from ESI. Perez, et al (27) concluded in their study that the severity of spinal stenosis as seen on imaging could not predict pain relief post-ESI. Our results show that spinal canal stenosis is not a significant predictor of significant pain relief. This may be due to our study's primary outcome was significant pain relief; clinically, 80% of patients over age 60 with imaging evidence of spinal stenosis are asymptomatic (24).

The disc size was divided into 3 grades by MSU classification; Grades 1 and 2 herniation were located below the intra-facet line. The distinction between them was whether the disc herniation extended up to 50%

Table 4. *Adverse effects happened in all groups during either the operation or follow-up period.*

	Group A (n = 28)	Group B (n = 32)	Group C (n = 33)
Dizziness and headache	0 (0%)	1 (3.1%)	0 (0%)
Nausea and vomiting	1 (3.6%)	0 (0%)	0 (0%)
Injection area swollen	0 (0%)	1 (3.1%)	0 (0%)
Facial flushing	0 (0%)	1 (3.1%)	1 (3%)
Dural sac punctured	1 (3.6%)	2 (6.2%)	2 (6%)
Epidural hematoma	0 (0%)	0 (0%)	0 (0%)
Epidural abscess	0 (0%)	0 (0%)	0 (0%)
Embolism from the steroid	0 (0%)	0 (0%)	0 (0%)
Total	2 (7.1%)	5 (15.6%)	3 (9%)

Group A: Methylprednisolone 10 mg; Group B: Methylprednisolone 20 mg; Group C: Methylprednisolone 40 mg; Data are reported as frequency (percentage).

of the distance from the nonherniated posterior aspect of the disc to the intra-facet line. Herniation of Grades 1 and 2 may not produce obvious pressure on nerve roots and the dural sac. Furthermore, the inflammatory pain caused by the migration of inflammatory cells and the release of mediators when the nucleus pulposus tissue is recognized by the immune system is often the main factor of acute radicular pain in patients with mild disc herniation. These 2 points may explain the nonsignificant effect of herniation size.

Chutatape, et al (28) found that fasting blood glucose was significantly higher than baseline one day post-ESI with 8 mg dexamethasone, while ACTH and cortisol were significantly decreased. It returned to a similar level as baseline at 7 and 21 days postinjection. A prospective study by Abdul, et al (29) showed that the levels of serum cortisol and ACTH in 30 patients who received ESI with 80 mg methylprednisolone decreased significantly at 14 days post-ESI, and returned to the baseline level at 28 days postinjection. The median inhibition time of the HPA axis was 14 days.

Habib, et al (17) reported that patients who received an ESI with 80 mg methylprednisolone were more likely to have secondary adrenal insufficiency than those with 40 mg at one week postinjection. Our study found that the changes in ACTH at one day post-ESI were similar in the 3 doses, but the changes in cortisol and FPG in the 40 mg dose were more significant than those in the 10 mg dose. This indicates that an increased steroid dose has little effect on the upstream hormones of the HPA axis. The study also found differences in changes in cortisol and FPG between 10 mg and 40 mg in patients without DM (17). This suggests that serum cortisol and FPG in patients without DM are more sensitive to the steroid dose than in patients with DM. This may be due to the fact that the patients with DM included in the trial were on regular drug therapy. The ESI treatments were always performed in the morning, and if the patient had abnormal FPG at night post-ESI, then hypoglycemic drugs or insulin therapy was given.

The most common adverse event during our trial was dural sac puncture, which was due to the narrowing of the epidural space in patients with hypertrophy of the ligamentum flavum and hyperplasia of facet joints. This forced the puncture path to be close to the dural sac. In addition, extensive calcification of the ligamentum flavum could result in the puncture needle being unable to pass through, so it was necessary to find the uncalcified area of the interlaminar space based on computed tomography results to plan the puncture path. However, this path often could not avoid the dural sac and enter the ventral epidural space, leading to dural sac puncture.

Limitation

Our study has some limitations. Firstly, this study is a single-center, prospective observational clinical trial. Patient selection had spatial aggregation, while grouping imbalance had confounding bias that may have affected the difference analysis among groups. Secondly, the follow-up measurement points set in the trial were few and close to the baseline; we could only monitor early results but not long-term efficacy. Additionally, many of the included cases were patients hospitalized with recurrent pain; their history may have formed pain sensitization, which can lead to underestimating ESI efficacy. Thirdly, we did not grade spinal canal stenosis and the intra-facet line disc location, and did not record the condition of ligamentum flavum hypertrophy, hyperplasia of facet joints, lumbar spondylolisthesis, painkiller usage, and other factors that could affect the efficiency of the regression model.

Conclusion

In summary, our study found that epidural injection with 20 mg or 40 mg of methylprednisolone had better short-term efficacy compared with 10 mg, but caused more significant changes in FPG and serum cortisol. The rate of short-term significant pain relief of 20 mg and 40 mg was similar, but the range of changes in FPG and serum cortisol was slightly smaller in 20 mg without statistical significance. Therefore, 20 mg can be used as a substitute dose for 40 mg in clinical practice. Additionally, our study suggests that baseline NRS-11 scores may be used as a predictor of effectiveness on pain relief post-ESI, and milder baseline pain intensity predicted better pain relief. However, our study has some limitations, and future studies should consider the grading of spinal canal stenosis and intra-facet line disc location, as well as other factors that may affect the efficiency of the regression model.

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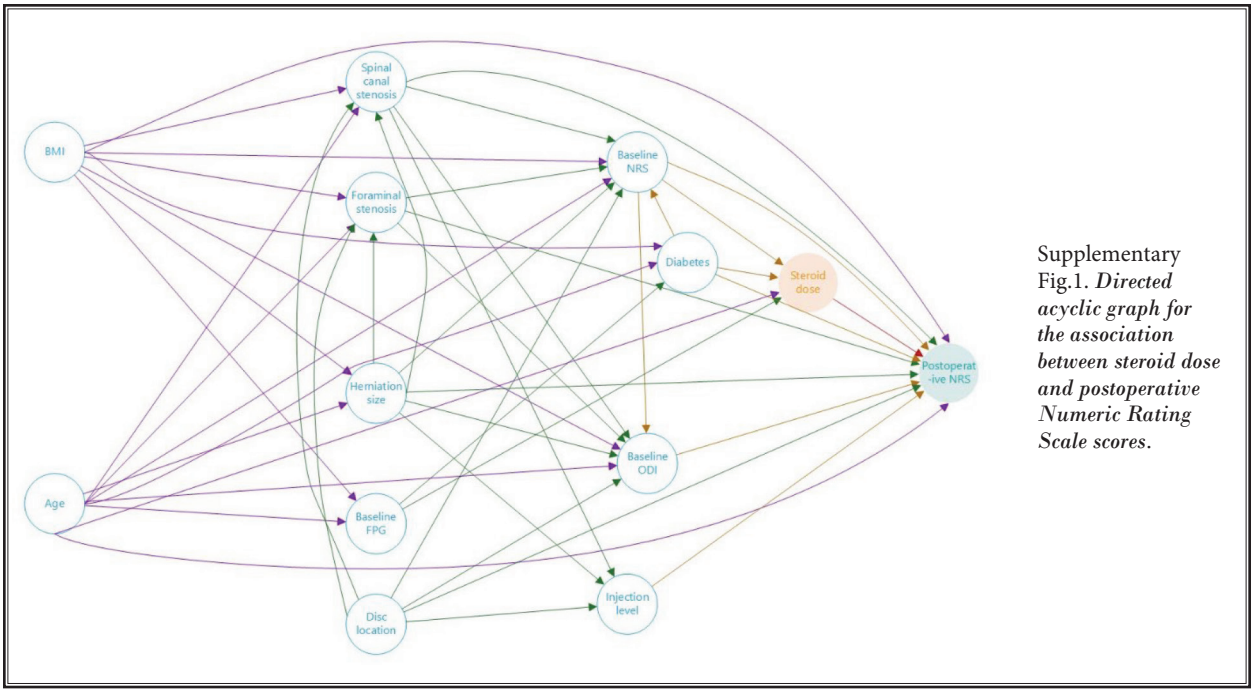

Supplementary Fig.1. *Directed acyclic graph for the association between steroid dose and postoperative Numeric Rating Scale scores.*

Supplementary Table 1. *Association of steroid doses (analyzed as ordinal variable) with ≥ 50% pain reduction at postinjection 7 days.*

	Adjusted Odds Ratio (95% CI)	*P* Value
	Steroid Doses	
Model 1	2.611 (1.457 - 4.679)	0.001
Model 2	2.908 (1.525 - 5.545)	0.001
Model 3	2.706 (1.373 - 5.33)	0.004

Model 1: Adjusted for age, body mass index, and gender.
Model 2: Adjusted for age, body mass index, gender, spinal canal stenosis, foraminal stenosis, herniation size, and disc location.
Model 3: Adjusted for spinal canal stenosis, herniation size, baseline Numeric Rating Scale score, baseline fasting plasma glucose, and diabetes mellitus.

Supplementary Table 2. *Association of steroid doses with ≥ 50% pain reduction at postinjection 7 days with all quantitative variable adjustments changing into ordinal variables.*

	Adjusted Odds Ratio (95%CI)		
	Model 1	Model 2	Model 3
10 mg vs 20 mg	3.355 (1.055 - 10.67)*	4.235 (1.199 - 14.96)*	6.107 (1.566 - 23.813)**
10 mg VS 40 mg	6.684 (2.099 - 21.28)**	8.522 (2.353 - 30.866)**	8.536 (2.271 - 32.085)**
40 mg VS 20 mg	0.502 (0.156 - 1.612)	0.497 (0.145 - 1.707)	0.715 (0.205 - 2.493)

Age changed into 6 grades: 18 – 30, 31 – 40, 41 – 50, 51 – 60, 61 – 70, and 71 – 80. Body mass index changed into 4 grades: < 18.5, 18.5 - 23.9, 24 - 27.9, and ≥ 28. Baseline Numeric Rating Scale scores changed into 2 grades: 4 – 6, and 7 – 10. Baseline Oswestry Disability Index scores changed into 5 grades: 0 - 20%, 21 -40%, 41 - 60%, 61 - 80%, and 81 - 100%. Baseline fasting plasma glucose changed into 3 grades: < 3.9, 3.9 - 6.1, and > 6.1. *: $P < 0.05$; **: $P < 0.01$.
Model 1: Adjusted for age, body mass index, and gender.
Model 2: Adjusted for age, body mass index, gender, spinal canal stenosis, foraminal stenosis, herniation size, and disc location.
Model 3: Adjusted for spinal canal stenosis, herniation size, baseline Numeric Rating Scale score, baseline fasting plasma glucose, and diabetes mellitus.