Hypothalamic Pituitary Adrenocortical Axis Suppression following a Single Epidural Injection of Methylprednisolone Acetate

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Background: Epidural injections (EIs) are the most commonly performed minimally invasive intervention in managing chronic low back pain (CLBP). There is inconsistency in data to accurately predict the degree of hypothalamic-pituitary-adrenal (HPA) axis suppression in patients receiving exogenous steroid therapy, especially in the form of epidural steroid injections (ESIs).

Objective: We aim to quantify the degree and duration of HPA axis suppression after a single ESI of 80 mg methyl prednisolone acetate in patients with CLBP.

Study Design: A single open-label prospective study.

Setting: An operating room of a tertiary care hospital.

Methods: Patients with CLBP and unilateral radicular pain were included in this study. An ESI of 80 mg of methylprednisolone acetate was administered in each patient. Blood samples for cortisol and adrenocorticotropic hormone (ACTH) were collected before the ESI and on days 7, 14, and 28 after the ESI. The patients’ pain levels were graded on the numeric rating scale (NRS) at baseline and on days 7, 14, 28, and 60 after the ESI in the pain clinic.

Results: A total of 30 patients were enrolled in this study. The median with interquartile range (IQR) serum cortisol level at baseline and on days 7, 14, and 28 after intervention were found to be 329.55 (208.49 – 399.48) nmol/L, 72.99 (52.95 – 119.82) nmol/L, 194.45 (73.88 – 292.52) nmol/L, and 302.56 (257.68 – 357.43) nmol/L, respectively. A significant decrease in the serum cortisol levels was observed on days 7 (P < 0.001) and 14 (P < 0.001). Twenty-six (87%), 13 (43%), and 2 (7%) patients had serum cortisol levels below normal (<170 nmol/L) on days 7, 14, and 28, respectively. HPA axis suppression was observed in all of the patients for a median (IQR) period of 14 days (range: 11–17 days).

Limitations: This study was an unblinded observational study. The effect of a single ESI was studied and the sample collection of day 21 serum cortisol and ACTH were passed over.

Conclusions: HPA axis function was suppressed after the ESI until day 14 and returned to the normal range by postoperative week 4.

Key words: Epidural injections, steroids, HPA, suppression, cortisol, ACTH

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ntervertebral disc herniation (IDH) with nerve irritation is one of the most common causes of lumbosacral radicular pain (LRP) (1). Radicular pain can arise as a result of nerve root inflammation with or without mechanical irritation. Inflammation within the epidural space and nerve roots, which can be provoked by a herniated disc or leakage of disc material from tears in the annulus fibrosus of a non-herniated disc, is a significant factor causing radicular pain (2). IDH results in the release of large amounts of phospholipase A₂ (3), which leads to the production of prostaglandins (4), resulting in inflammation, sensitization of nerve endings, and pain generation (2).

Epidural injections (EIs) are the most commonly performed minimally invasive intervention in managing chronic low back pain (CLBP) with LRP. Reportedly, there has been a 165% increase in EIs from 2000 to 2013 in Medicare beneficiaries (1,5,6). Steroids alone or in combination with local anesthetic are the most commonly used injectate for EIs (1,5-9). The analgesic effects of corticosteroids are most likely related to the reduction of inflammation by inhibiting the synthesis or release of proinflammatory mediators, inhibiting neural transmission in nociceptive C fibers and causing a reversible local anesthetic effect (2,10,11).

Although interventional pain management with epidural steroid injection (ESI) is often practiced, its effect on the endocrine system has not yet been evaluated extensively. Few complications of ESI that can be directly attributed either to the chemistry or pharmacology of steroids are mentioned in the literature (12). Only a few case reports and series reporting variable degree and duration of hypothalamic-pituitary-adrenal (HPA) axis suppression with ESI are available. These studies are limited by small sample sizes or using variable doses and frequencies of ESI (13-16).

Case reports of severe HPA axis suppression leading to Cushing’s syndrome are also reported after an ESI (17,18). The duration of corticosteroid therapy, highest used dosage, and total cumulative corticosteroid dose are proposed to be important predictors of HPA axis suppression. There is inconsistency in data to accurately predict the degree of HPA axis suppression in patients receiving exogenous steroid therapy, especially in the form of ESI (19).

To the best of our knowledge, no study is available in the Indian population evaluating the effect of a single lumbar ESI on the HPA axis. Hence, we planned to conduct the present study to quantify the degree and duration of HPA axis suppression after a single ESI of 80 mg methylprednisolone in patients with CLBP.

**Methods**

**Study Design**

This is a single-arm, open-label, interventional trial conducted in the pain clinic of a public tertiary care hospital in North India. The Consolidated Standards of Reporting Trials (CONSORT) guidelines and Principles of the Declaration of Helsinki were followed (20). The study was approved by the Institute Ethics Committee (NK1059/MD13602-603) and registered with the Clinical Trial Registry of India (CTRI/2015/01/005383). This was an investigator-initiated study, and only intramural, institutional resources were utilized.

**Participants**

Patients of the American Society of Anesthesiologists-I (ASA-I) physical status of either gender over 18 years old with CLBP and unilateral LRP for at least 3 months duration and not showing any improvement with previous medications for pain relief (nonsteroidal anti-inflammatory drugs, pregabalin, gabapentin) and physical exercises were assessed for study inclusion. All of the patients were evaluated with imaging modalities such as magnetic resonance imaging to confirm the exact site and extent of lumbar disc pathology.

Patients were excluded if they had coagulopathy, infection at the procedure site, allergy to corticosteroids, low baseline cortisol levels, endocrine disorders, history of corticosteroid treatment in the preceding year, chronic medical illnesses (diabetes, hypertension, heart failure, renal disease, liver disease, etc.), and severe stress in the preceding month. In addition, grossly obese patients, patients taking contraceptives, and those working night shifts were excluded. Women who were pregnant, lactating, or intending to become pregnant were also excluded. Moreover, patients who had consumed alcohol 12 hours before sampling or food one hour before sampling were excluded.

**Study Interventions and Procedure**

Before intervention, intravenous access and standard monitoring were established. The baseline heart rate, non-invasive blood pressure, and oxygen saturation of each patient were noted. All of the procedures were performed under C-arm fluoroscopic guidance with the patient in prone position, using the parasagittal interlaminar approach as described previously.
The intervertebral level and the site for drug administration were determined according to the clinical examination and the results of diagnostic imaging studies. The maximum affected level was selected if multiple discs were involved. An 80 mg methylprednisolone acetate (DEPO-MEDROL™, Pfizer Ltd., Mumbai, India) diluted in 6 mL of saline (total volume 8 mL) was delivered at the site of pathology. The patients were kept under close observation for at least 30 minutes post-procedure.

Assessment and Follow-up
The baseline assessment included body weight, blood pressure, numeric rating scale (NRS) pain score (0 – 10; 0 being no pain and 10 being the worst pain imaginable), cortisol and adrenocorticotropic hormone (ACTH) levels, and fasting blood sugar (FBS).

During the study period, samples for cortisol and ACTH were collected before the ESI and on days 7, 14, and 28 after the ESI. Additionally, FBS was also monitored on day 28. The patients were followed-up on days 14, 28, and 60 postoperatively in the pain clinic for pain assessment. The patients were instructed to give their sample for analysis between 8:00 a.m. and 9:00 a.m.

Post-Intervention Medications
All medications for pain relief, physiotherapy, and specific back exercises were continued.

Plasma Cortisol and ACTH Levels Assessment
Fasting plasma ACTH and cortisol levels were estimated in the morning samples by electrochemiluminescence immunoassay (ECLIA) (E-2010, Roche Diagnostics, Germany), using kits, calibrators, and controls from the same manufacturer. Peripheral blood samples were obtained in sterile 3.0 mL K2 EDTA vacutainer tubes (BD Biosciences, US). The plasma was separated by centrifugation. For ACTH determination, the cold chain was maintained throughout, from sampling to processing. Briefly, ACTH was determined by a sandwich assay, using 2 monoclonal antibodies. The first antibody was biotinylated and specific for ACTH, while the second antibody was substrate labeled and specific for the C-terminal region. The assay had a measuring range of 0.5 – 1750 nmol/L (intra-assay CV, 1.4% and inter-assay CV, 1.6%).

Primary and Secondary Outcomes
The primary outcome of this study was the morning plasma cortisol and ACTH levels on day 7. The secondary outcomes were the plasma cortisol and ACTH levels on days 14 and 28, the NRS scores on days 14, 28, and 60, and the body weight and FBS levels on days 7, 14, and 28.

Sample Size Calculation
The normal morning cortisol concentrations in our laboratory are between 171 – 536 nmol/L. Patients who had serum cortisol levels less than 170 nmol/L on day 7 following ESI were considered to have developed secondary adrenal insufficiency (SAI). Taking evidence from a previous study (16), the incidence of SAI with 80 mg of epidural methylprednisolone is reported to be 86% at day 7. We estimated that to detect the incidence of SAI in the present study to be around 80% with power of 80% and level of significance of 0.05. About 24 patients were required to be recruited for our study.

Statistical Analysis
Data were represented as either mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables and number with percentages for categorical variables. All observations were recorded in a standardized data collection sheet. The paired t-test, Mann-Whitney, and Fisher’s exact tests were used to compare continuous and categorical parameters, respectively, in all of the study patients. The Wilcoxon signed-rank test was used to compare day 0 (just prior to the ESI) serum cortisol and ACTH levels with post-procedure days 7, 14, and 28 samples. All of the patients attended all of the follow-up visits. In terms of clinical response, ≥ 50% reduction in the NRS score at each time-point compared with the baseline level was considered a favorable clinical response. Data were analyzed statistically, with 0.05 being a level of significance. Statistical analysis was carried out using SPSS Version 15.0 (SPSS Inc., Chicago, IL).

Results
This study was conducted between April 2014 and February 2015. The flow chart of patients is provided in Fig. 1. Of the 78 patients screened, 40 met the inclusion criteria. Eight patients refused consent.
Fig. 1. Flow chart of participants. The values of cortisol and ACTH are expressed in median (IQR). ACTH = adrenocorticotropic hormone, ESI = epidural steroid injection.
to participate, and 2 patients were excluded before the ESI as they had low baseline cortisol levels. Hence, a total of 30 patients were included for the study. All of the patients included in the study completed the study protocol.

The mean (SD) age of the included patients was 49.5 (12.1) years and 47% of the patients were men. Although the height and weight of the included male patients was significantly higher \( (P = 0.002 \text{ and } 0.005) \), the body mass index was comparable in both of the genders (0.52). All of the included patients had their systolic blood pressure, diastolic blood pressure, FBS, and serum cortisol and ACTH levels in the normal range, and both men and women had comparable values, as shown in Table 1.

### Primary Outcome

**Changes in Serum Cortisol Concentration**

The median (IQR) serum cortisol level at baseline (day 0, prior to the ESI), days 7, 14, and 28 were found to be 329.55 (208.49 – 399.48) nmol/L, 72.99 (52.95 – 119.82) nmol/L, 194.45 (73.88 – 292.52) nmol/L, and 302.56 (257.68 – 357.43) nmol/L, respectively. A significant decrease in the serum cortisol levels was observed on days 7 \( (P < 0.001) \) and 14 \( (P < 0.001) \) compared to the baseline serum cortisol levels, whereas day 28 serum cortisol levels were comparable with the baseline values \( (P = 0.49) \) (Fig. 2). Twenty-six (87%), 13 (43%), and 2 (7%) patients had serum cortisol levels below normal (< 170 nmol/L) on postoperative days 7, 14, and 28, respectively. In total, 28 out of 30 patients had recovered from acute HPA axis suppression and reached baseline cortisol concentrations within 1 month (Table 2). HPA axis suppression was observed in all of the patients for a median (IQR) period of 14 (11–17) days.

**Changes of Serum ACTH Concentration**

The median (IQR) serum ACTH level at baseline (day 0, prior to the ESI), days 7, 14, and 28 was found to be 29.26 (15.92 – 46.84) pg/mL, 8.70 (1.97 – 18.34) pg/mL, 15.96 (10.82 – 26.07) pg/mL, and 20.06 (15.88 – 41.37) pg/mL, respectively. A significant decrease in the serum ACTH levels was observed on days 7 \( (P < 0.001) \) and 14 \( (P = 0.03) \) compared to the baseline serum ACTH levels, whereas the day 28 serum ACTH levels were comparable with the baseline values \( (P = 0.74) \) (Fig. 3).

**NRS Scores for Pain**

A repeated measure analysis showed that the NRS scores significantly decreased after the ESI at days 14, 28, and 60 compared to baseline \( (P < 0.0001 \text{ for all 3 comparisons}) \). Considering ≥ 50% reduction in the NRS score as a favorable clinical response, 21 (70%), 26 (87%), and 10 (33%) patients had achieved favorable pain relief at days 14, 28, and 60 days, respectively (Fig. 4).

### Other Parameters

No significant differences were observed between baseline and day 28 values in bodyweight, systolic blood pressure, diastolic blood pressure, and FBS (Table 3).

**Discussion**

The results of the present study showed that administration of exogenous steroids in the form of an ESI...
Fig. 2. Serum cortisol changes over 4 weeks. Box plot showing distribution of serum cortisol levels at day-0 (just prior to epidural 80 mg of methylprednisolone acetate injection) and at day 7, 14, and 28. The central line of box represents median value and lower and upper borders of the box represent quartile 1 (Q1) and 3 (Q3). The upper and lower whiskers = Q3 + 1.5 interquartile range (IQR) and Q1 - 1.5 IQR, respectively. Numbered small circles = serial numbers of patients tested for cortisol level with a value higher than the upper whisker. P values represent comparison with baseline (day 0) values, computed using Wilcoxon sign rank test.

Table 2. Serum cortisol and ACTH levels.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 28</th>
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<tbody>
<tr>
<td><strong>Serum Cortisol (nmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>321.29 (117.34)</td>
<td>98.91 (68.13)</td>
<td>197.72 (133.34)</td>
<td>303.11 (84.54)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>329.5 (208.49 – 399.48)</td>
<td>72.99 (52.95 – 119.82)</td>
<td>194.45 (73.88 – 292.52)</td>
<td>302.56 (257.68 – 357.43)</td>
</tr>
<tr>
<td>&lt; 170 nmol/L</td>
<td>-</td>
<td>26 (87)</td>
<td>13 (43)</td>
<td>2 (10)</td>
</tr>
<tr>
<td><strong>Serum ACTH (pm/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.39 (18.54)</td>
<td>13.39 (14.63)</td>
<td>20.94 (17.75)</td>
<td>29.65 (21.16)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>29.26 (15.92 – 46.84)</td>
<td>8.70 (1.97 – 18.34)</td>
<td>15.96 (10.82 – 26.07)</td>
<td>20.06 (15.88 – 41.37)</td>
</tr>
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</table>

White row indicates number (%) of patients having serum cortisol levels of < 170 nmol/L. SD = standard deviation; IQR = interquartile range; ACTH = adrenocorticotropic hormone.
of methylprednisolone acetate at a dose of 80 mg, resulted in acute HPA axis suppression leading to secondary adrenal insufficiency in the majority of the patients at day 7 (~87%). There was a gradual recovery of the adrenal gland, and by day 28 following the intervention, only 2 patients had SAI at the 30-day follow-up. We found the median duration of HPA axis suppression to be 14 days after a single lumbar ESI of 80 mg methylprednisolone in patients with CLBP and radicular pain.

ESIs are being used routinely for CLBP management, but its effect on the endocrine system has not been evaluated extensively. The major theoretical complications of steroid administration include suppression of the HPA axis, hypercorticism, Cushing’s syndrome, osteoporosis, avascular necrosis of bone, steroid myopathy, epidural lipomatosis, weight gain, fluid retention, and hyperglycemia (22).

To the best of our knowledge, the effect of an ESI on the HPA axis is not studied to date in the Indian population. Few studies evaluating the effect of ESIs on the HPA axis have been reported, but the majority of these studies has either used a small sample size or has...
used variable doses and frequencies of ESIs.

Kay et al (13), in a small series of 14 patients (7/14 received intravenous midazolam additionally), have reported that 3 doses of ESI administered weekly over 3 weeks are reported to cause acute dramatic HPA axis suppression for about 1 month. They also reported the accentuated suppression with midazolam premedication. All of the patients recovered from HPA axis suppression by 3 months. Jacob et al (14) evaluated the effect of a single extradural injection of 80 mg dexamethasone on the HPA axis in 12 patients with chronic sciatica. They also reported marked suppression in all of the patients until 3 weeks and a remarkably diminished response of the adrenal cortex to cosyntropin. Plasma methylprednisolone levels were also measured and were found to be undetectable (< 30 nmol/L) in all of the patients, indicating that the systemic absorption of this steroid was not responsible for the observed HPA axis suppression. It is possible that following extradural injection of steroid suspension, high concentration is quickly achieved in the subarachnoid space, and rapid absorption in the central nervous system tissue resulted in hypothalamic suppression.

Choon et al (15) studied the period of HPA axis suppression by salivary cortisol measurements after a single ESI of 40 mg triamcinolone in 8 patients with IDH and spinal stenosis. The special characteristic of this study was the adoption of a noninvasive approach to measure serum cortisol. Cortisol concentrations were assessed both before (day 0) and after the ESI (days 1, 3, 5, 7, 14, 21). They observed HPA axis suppression in all of the patients after ESI. All of the patients recovered from this suppression in a mean (SD) duration of 19.4 (8.3) days. Five out of 8 patients reached baseline salivary cortisol concentration within the clinical trial period.

In a recent study, Habib et al (16) sheds light on acute HPA axis suppression at 1 week after an ESI of 40 mg and 80 mg methylprednisolone in 2 groups of 21 patients each. The patients in both of the groups were tested for adrenal cortex function using 1 µg ACTH stimulation test on day 0 (just prior to ESI) and weeks 1, 3, and 4 post-intervention. The proportion of patients developing SAI in the 80 mg group was ~86%, ~22%, and ~17%, whereas in the 40 mg group it was ~53% (P = 0.024), 15% (P = 0.874), and ~12% (P = 0.715) at
weeks 1, 3, and 4, respectively. Also, the 80 mg group had significantly lower serum cortisol concentrations at weeks 1 and 3 when compared with the baseline concentrations, while the 40 mg group had a significantly lower serum cortisol concentration at only week 1 as compared with the baseline concentration. The clinical outcome was found to be favorable with a higher dose.

Hsu et al (23) compared plasma cortisol and ACTH profiles of 2 doses of triamcinolone (40 mg and 80 mg) of a single EI. They concluded that 40 mg of triamcinolone decreased plasma cortisol for only 24 hours markedly, whereas 80 mg of triamcinolone led to HPA axis suppression up to 14 days post-treatment. The patients recovered in an average duration of 35 days in both groups.

Besides these previous studies, at least 6 biochemically proven cases of iatrogenic Cushing's syndrome have been reported as complications of ESI (17,18,24-27). These reports indicated that pharmacologic doses of exogenous epidural corticosteroids do suppress the HPA axis by inhibiting ACTH secretion.

The present study is in line with earlier studies showing significant HPA suppression after a single ESI of 80 mg methylprednisolone acetate in steroid-naïve patients. The effect of a single ESI on the HPA axis lasts for around 3 – 4 weeks, with 98% of patients recovering from it within 4 weeks. However, the median (IQR) duration of suppression in the present study was 14 (11 – 17) days. The results of this study have far-reaching clinical impact. There are as such no clear guidelines regarding the dosing interval and maximum number of ESIs to be administered (28). Some expert recommendations promote giving up to 3 injections within 1 year with a minimum of 30 days between injections. This study supports the fact that more frequent injections are not recommended due to concerns about HPA axis suppression after ESIs.

The American Society of Interventional Pain Physicians- Interventional Pain Management 2009 Guidelines have clearly mentioned that there is no basis for reported assumptions and limitations on ESI doses or frequency, and the administration must be based solely on the patient’s response, safety profile of the drug, experience of the patient, and pharmacologic and chemical properties such as the duration of action and suppression of adrenals. However, they have also recommended that ESIs should not be given more frequently than every 1 to 2 weeks during the diagnostic phase and thereafter every 2 months (29). The results of this study emphasize that the dosing interval should be kept at least 3 – 4 weeks apart as 98% patients had their serum cortisol levels within normal range by 4 weeks.

The total number of ESIs required in an individual patient has not been clearly defined in the literature, however some patients may improve after only 2 – 3 injections (28,29). Ackerman and Ahmad (30) reported that patients treated with repeated injections using interlaminar and caudal routes had increased efficacy. They hypothesized that the increased efficacy could be related to repeated systemic uptake from the epidural veins in the epidural space and blood vessels in the subarachnoid space after passive diffusion of the steroid across the duramater (31).

However, repeat ESI administration is required in case the initial administration does not bring effective pain relief (20,21,32). Ultimately, to predict the systemic effects of ESIs, it is fundamental to define the timing, frequency, and doses of glucocorticoid administrations; indeed, the majority of daily clinical practice is based on empirical clinical protocols (22).

Adrenal cortical secretion follows the circadian rhythm, and plasma cortisol concentrations also vary by age, gender, and season (33). Peak concentrations are achieved in the morning and are the lowest around midnight (34). Therefore, normal morning serum cortisol measurements are useful diagnostic indicators of adrenal suppression.

**Strength**

We studied 80 mg methylprednisolone acetate, as it is the most commonly used drug and dose in our institute for interlaminar EIs. In fact, while examining the practice pattern in the use of ESI, it is shown that the most commonly used agents for administration in neural blockade is methylprednisolone acetate (82% of practitioners), followed by triamcinolone (13%) and betamethasone (5%). Moreover, the study was adequately powered and the standard method of cortisol measurement was used.

**Limitations**

There are certain limitations that have to be taken into account while analyzing the results. First, this was an unblinded observational study. However, the end-point of the study was laboratory data that are objective, and the results might not be affected by the unblinded observational nature of this study. Second, the effect of a single ESI was studied; hence results cannot be extrapolated to patients receiving more than one ESI. Third, as the primary focus of this study was to
ascertain changes of the HPA axis function and monitor the trends in these variations, serum cortisol and ACTH were serially monitored without looking for adrenal insufficiency using an ACTH stimulation test. Fourth, due to the invasive nature of the sample collection, the week 3 serum cortisol and ACTH levels were passed over. This was done to increase patient compliance. Fifth, we do not know exactly at what time the cortisol concentration reached to the initial value, whereas we only determined that these concentrations decreased at weeks 1 and 2 and returned to the baseline levels in 28 patients at week 4.

**Conclusion**

We concluded from our study that after a single ESI (methyl prednisolone acetate 80 mg), there is a suppression of the serum cortisol and ACTH concentration for about 2 weeks, which returns to baseline at week 4. Supplementary corticosteroids are therefore needed during or prior to major stressful events (including non-minor surgical procedures) that occur in patients within at least the first 3 weeks after an epidural corticosteroid injection, preferably for those patients who receive an 80 mg dose of methylprednisolone acetate. Ideally, an ACTH stimulation test done beyond 1 month (6 – 8 weeks) following an epidural corticosteroid injection may shed more light on the time to complete recovery of the adrenal glands following this injection (35). The scope of this study can be effectively enhanced further by ensuring the use of noninvasive, cost-effective, and easy methods of sampling measurements (e.g., salivary cortisol) to make it more patient-compliant.

**References**


17. Leary J, Swislocki A. Hypothalamic-pituitary-adrenal suppression and iatrogenic Cushing’s syndrome as a complication of epidural steroid injections. *Case
HPA Axis Suppression following Epidural Injection of Methylprednisolone Acetate


