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Original Article

Epidural dexamethasone injections in diabetic patients under perioperative glycemic control

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Abstract: Introduction: Diabetic patients might be more susceptible to systemic side effects caused by corticosteroids used in ESI, compared to non-diabetic patients. Therefore, controlling hyperglycemic excursion for diabetic patients that have been exposed to glucocorticoids is recommended. However, the beneficial effects of perioperative glycemic control via epidural steroid injections (ESI) have rarely been reported. The current study evaluated the effects of epidural dexamethasone injections in diabetes mellitus (DM) patients under perioperative glycemic control. Materials and methods: Patients with and without DM, undergoing epidural dexamethasone injections, were categorized into DM (n=14) and non-DM groups (n=48). Patients with elevated fasting plasma glucose (FPG) levels the next day were categorized into FPGUP subgroups, in both DM (FPGUP-DSG, n=5) and non-DM groups (FPGUP-NSG, n=36). For patients in the DM group, regular insulin (8 IU of Humulin R in 1000 mL of 5% D/S solution) was administered intravenously the day before and the day of ESI. Blood tests were performed preoperatively, one day postoperatively (POD1), and on the 10th day (POD2). Questionnaires regarding pain and disability were completed, preoperatively and postoperatively. Results: Preoperative FPG was significantly elevated at POD1, while returning to baseline at POD2 in the non-DM group. However, values did not change in the DM group. Preoperative cortisol significantly decreased at POD1 and returned at POD2 in both groups and subgroups. Clinical scores significantly improved, postoperatively, in non-DM and DM groups, as well as the FPGUP-NSG group, but not in the FPGUP-DSG group. Conclusion: Pronounced blood glucose excursion and hypocortisolism after ESI in DM patients can be controlled by administering dexamethasone and adding perioperative insulin. However, DM patients with uncontrolled hyperglycemia that receive insulin could be at risk for failed ESI.

Keywords: Epidural steroid injection, dexamethasone, diabetes mellitus, glycemic control, insulin

Introduction

Systemic and non-localized adverse effects of corticosteroids are common in patients receiving corticosteroids in high doses or for long periods of time [1]. Through epidural steroid injections (ESI), high-dosed steroids are commonly administered to patients. Thus, ESI can cause systemic side effects.

Dexamethasone, a non-particulate steroid, is preferred for trans-foraminal epidural injections [2], preventing unintended embolic side effects [3, 4]. However, the systemic effects of dexamethasone following epidural injections are not well known, compared to particulate steroids.

Elevated and less-controlled blood glucose and depression of the hypothalamus-pituitary-adrenal axis (HPAA) for several days to weeks are typical systemic effects that follow local injections of corticosteroids into joints or epidural spaces. Patients with these side effects may suffer from acute hyperglycemia and adrenal insufficiency and may be exposed to infection risks [5, 6]. Diabetic patients might be more susceptible to systemic side effects caused by corticosteroids used in ESI, compared to non-diabetic patients [6, 7]. Controlling hypergly-

cemic excursion for patients that have been exposed to glucocorticoids is recommended [1, 8]. However, to the best of our knowledge, the beneficial effects of perioperative glycemic control in ESI have not yet been reported.

The purpose of this study was to report the effects of ESI with dexamethasone under perioperative glycemic control on improving spinal symptoms, glucose metabolism, and HPAA function, examining clinical and basic blood studies in patients with and without diabetes mellitus (DM).

Methods

Participants

Patients with degenerative lumbar spinal disease undergoing ESI using dexamethasone in 2016 and followed-up in the Outpatient Clinic for a minimum of 6 months were included. All patients provided informed consent. The current study was approved by the Institutional Review Board (UC15RISI0186).

DM patients already receiving glycemic medication, with DM criteria (HbA1C ≥6.5% or fasting plasma glucose (FPG) ≥126 mg/dL) [9] according to blood tests performed within 4 weeks of the ESI index procedure preoperatively, were selected for the DM group. Patients with HbA1C ≤8.0% and those with blood glucose well-controlled by hypoglycemic medication, as determined by the endocrinologist, were also included in the DM group. All patients in the DM group maintained hypoglycemic medications until the index ESI. Patients not included in the DM group were assigned to the non-DM group.

ESI procedures

Patients were admitted to the hospital one day before the ESI and were discharged the day after. Each patient underwent multiple transforaminal epidural injections for corresponding spinal stenosis lesions. Next, they received caudal epidural injections through the sacral hiatus using the epidural catheter (Abel epidural catheter system, GS Medical, South Korea), under C-arm radiographic guidance.

A mixture of 10 mg dexamethasone (2 cc), 2% lidocaine (2 cc), and 0.9% normal saline (10 cc) was used as for therapeutic injections. For each transforaminal injection, therapeutics were injected with a 22-gauge Tuohy needle at the pathologic segment. During caudal injections, the rest of the mixture was injected at the major pathology site, while the epidural catheter was advanced from the sacral hiatus.

Perioperative glycemic control

For patients in the DM group, regular insulin (RI, 8 IU of Humulin R mixed in 1000 mL of 5% D/S solution) was administered, intravenously, to control blood glucose excursion overnight the day before and the day after ESI. The day after ESI, additional insulin was administered if postprandial blood sugar tests (BST), after dinner, showed a result over 200 mg/dL. In this study, 4 IU of RI was also given to two patients. From the second day following ESI, patients in the DM group restarted their own hypoglycemic agents.

Laboratory and clinical tests

For each patient, blood tests were performed within 4 weeks of ESI preoperatively (preoperative day, PRD), the day after ESI (postoperative day 1, POD1), and the 10th day after ESI (POD2), in a morning fasting state. In each blood test, parameters for glucose metabolism (FPG) and HPAA (Hypothalamic-Pituitary-Adrenal Axis) function (Cortisol) were included.

To test the clinical effectiveness of ESI, each patient completed a questionnaire concerning pain [Visual Analogue Scale (VAS) for lower back pain (LBP) and leg pain] and disability [the Oswestry Disability Index (ODI)] for spinal disease. These were completed before the procedure and the day of the 2nd postoperative blood test (POD2).

Statistical analyses

For each parameter, repeated measures ANOVA was performed, with time points (PRD, POD1, and POD2) as a within-subject variable. Parameters demonstrating significant changes were followed by post-hoc analyses. For each parameter in the questionnaire, pairwise t-tests were performed, comparing preoperative and postoperative values. Finally, parameters (lab and clinical tests) of the two groups (non-DM and DM), at each time point, were compared using one-way ANOVA.

Table 1. Demographic data for non-DM (NDG) and DM (DMG) groups and subgroups (FPGUP-NSG and FPGUP-DSG)

	NDG	DMG	P NDG vs. DMG	P FPGUP-NSG vs. -DSG
Patients [N (% in each group)]	48 (100)	14 (100)	0.010*	
FPGUP subgroups	36 (75)	5 (35.7)		
Age [years]	58.1 ± 14.3	57.3 ± 13.7	0.850	
FPGUP subgroups	57.6 ± 13.4	57.6 ± 12.0		0.999
POD2 [days]	9.5 ± 2.2	9.8 ± 1.6	0.623	
FPGUP subgroups	9.3 ± 1.6	10.4 ± 2.4		0.193
Sex [N (% in each group)]			0.078	
Male	19 (39.6)	2 (14.3)		
Female	29 (60.4)	12 (85.7)		
FPGUP subgroups				
Male	16 (44.4)	0 (0)		0.056
Female	20 (55.6)	5 (100)		
HbA1C [%]	5.5 ± 0.4	7.0 ± 0.9	<0.001*	
FPGUP subgroups	5.5 ± 0.4	7.2 ± 0.7		<0.001#

*significant differences between NDG and DMG; #significant differences between FPGUP-NSG and -DSG.

Table 2. Preoperative and postoperative values of FPG and cortisol in both non-DM (NDG) and DM (DMG) groups, as well as in subgroups (FPGUP-NSG and FPGUP-DSG)

	NDG			DMG			
	Mean ± SD	N	P PRD vs. POD1 PRD vs. POD2	Mean ± SD	N	P PRD vs. POD1 PRD vs. POD2	P NDG vs. DMG
FPG [mg/dL]							
PRD	99.4 ± 12.2	48		158.1 ± 63.7	14		<0.001#
POD1	115.4 ± 20.8	48	<0.001*	155.1 ± 54.2	14	0.598	0.009#
POD2	97.4 ± 19.5	48	0.539	139.6 ± 40.8	14	0.314	0.002#
FPGUP subgroups							
PRD	96.9 ± 10.8	36		135.2 ± 23.3	5		<0.001#
POD1	119.9 ± 19.4	36	<0.001*	182.6 ± 48.4	5	0.044	0.009#
POD2	98.2 ± 21.4	36	0.680	152.5 ± 64.6	5	0.477	0.002#
Cortisol [ug/dL]							
PRD	15.5 ± 7.9	46		15.9 ± 9.7	14		0.841
POD1	0.9 ± 0.9	46	<0.001*	2.3 ± 3.9	14	0.001*	0.035#
POD2	14.8 ± 7.2	46	0.497	15.3 ± 10.1	14	0.786	0.534
FPGUP subgroups							
PRD	15.2 ± 7.8	36		18.0 ± 8.4	5		0.806
POD1	0.9 ± 0.6	36	<0.001*	1.7 ± 1.6	5	0.010*	0.046#
POD2	14.2 ± 6.4	36	0.436	22.9 ± 9.4	5	0.593	0.025#

*significant differences between PRD and POD1 or PRD and POD2 in each group and subgroup; #significant differences between NDG and DMG.

Patients demonstrating FPG elevation at POD1 were categorized into FPGUP subgroups, in both non-DM (FPGUP-NSG) and DM (FPGUP-DSG) groups. All statistical analyses performed for non-DM and DM groups were repeated for FPGUP-NSG and FPGUP-DSG.

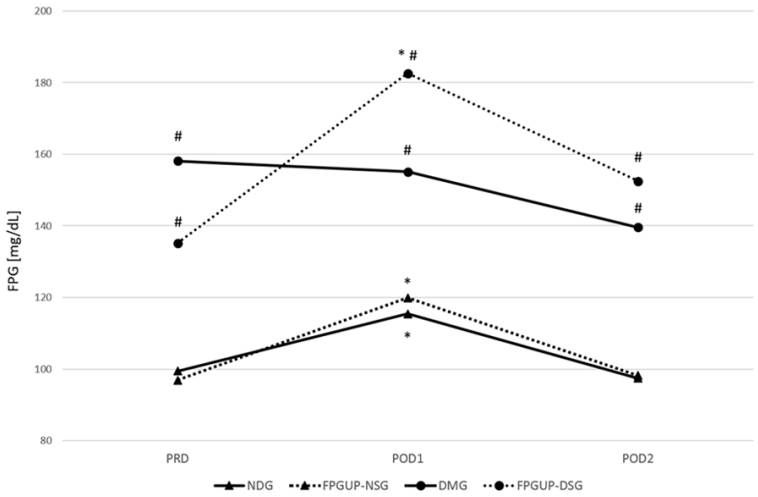

Figure 1. Preoperative FPG was significantly elevated at POD1 (*) and returned to baseline at POD2 in the non-DM group (NDG), FPGUP-NSG group, and FPGUP-DSG group. FPG values were not significantly changed in the DM group (DMG). Elevation of FPG in the FPGUP-DSG group was higher than increases in NDG and FPGUP-NSG groups. FPG values in DMG and FPGUP-DSG groups were significantly greater than those in NDG and FPGUP-NSG groups, at all time-points, respectively (#).

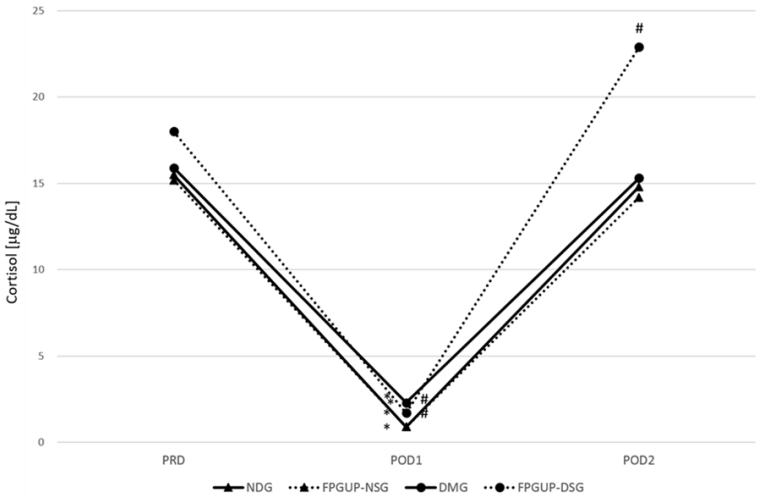

Figure 2. Preoperative cortisol values were significantly decreased at POD1 (*) and returned to baseline at POD2 in both groups and subgroups. Cortisol values in the DM group (DMG) were significantly greater than those in the non-DM group (NDG) at POD1 (#). Cortisol values in the FPGUP-DSG group were significantly greater than those in the FPGUP-NSG group at POD1 and POD2 (#).

Results

Demographics

There were 48 patients in the non-DM group and 14 in the DM group. The mean number of days after ESI at POD2 was 9.5 ± 2.2 in the non-DM group and 9.8 ± 1.6 in the DM group. These values were not significantly different between the two groups (**Table 1**).

Glucose metabolism

In the non-DM group, preoperative values of FPG were significantly elevated at POD1. Values decreased to baseline at POD2. However, in the DM group, preoperative values of FPG did not significantly change at POD1 and POD2. FPG values were significantly greater in the DM group than in the non-DM group at all time-points. In the FPGUP-NSG group, preoperative values of FPG were significantly elevated at POD1, but values were restored at POD2. In the FPGUP-DSG group, preoperative FPG was significantly elevated at POD1, but restored at POD2. FPG values were significantly greater in the FPGUP-DSG group than in the FPGUP-NSG group at all time-points (**Table 2**, **Figure 1**).

HPAA function

Preoperative cortisol values were significantly decreased at POD1. However, values were restored at POD2 in both non-DM and DM groups. Cortisol values in the DM group were significantly greater than those in the non-DM group at POD1. Preoperative cortisol values significantly decreased at POD1, but were restored at POD2 in FPGUP-NSG and FPGUP-DSG groups. Cortisol values in the FPGUP-DSG group were significantly greater than those in the FPGUP-NSG group at POD1 (**Table 2**, **Figure 2**).

Clinical parameters

Preoperative VAS scores for LBP and leg pain were significantly improved, postoperatively, in non-DM and DM groups and the FPGUP-NSG

Table 3. Preoperative and postoperative values for pain (LBP and leg pain) and disability in both non-DM (NDG) and DM (DMG) groups, as well as in subgroups (FPGUP-NSG and FPGUP-DSG)

	NDG			DMG			P
	Mean ± SD	N	P PRD vs. POD2	Mean ± SD	N	P PRD vs. POD2	NDG vs. DMG
VAS (LBP)							
PRD	5.6 ± 2.9	48		5.1 ± 3.5	14		0.013#
POD2	3.1 ± 3.1	48	<0.001*	2.5 ± 2.6	14	0.019*	0.095
FPGUP subgroups							
PRD	5.9 ± 2.6	36		5.8 ± 4.3	5		0.917
POD2	3.5 ± 3.3	36	<0.001*	4.3 ± 3.3	5	0.495	0.669
VAS (Leg Pain)							
PRD	6.1 ± 3.3	48		5.1 ± 3.3	14		0.284
POD2	2.6 ± 2.5	48	<0.001*	2.9 ± 2.4	14	0.005*	0.878
FPGUP subgroups							
PRD	6.3 ± 3.2	36		7.3 ± 3.2	5		0.617
POD2	2.7 ± 2.7	36	<0.001*	4.8 ± 1.3	5	0.155	0.147
ODI							
PRD	43.8 ± 23.0	48		51.0 ± 23.2	14		0.497
POD2	25.2 ± 19.0	48	<0.001*	30.3 ± 21.6	14	0.002*	0.401
FPGUP subgroups							
PRD	40.6 ± 23.3	36		70.7 ± 20.1	5		0.026#
POD2	25.0 ± 20.4	36	<0.001*	50.7 ± 13.1	5	0.146	0.021#

*significant differences between PRD and POD1 or PRD and POD2 in each group and subgroup; #significant differences between NDG and DMG.

group, but not in the FPGUP-DSG group (**Table 3**, **Figures 3**, **4**). Preoperative ODI scores significantly improved, postoperatively, in non-DM and DM groups and the FPGUP-NSG group, but not in the FPGUP-DSG group. ODI scores were not significantly different between non-DM and DM groups, at all time points, but were significantly higher in the FPGUP-DSG group than the FPGUP-NSG group at PRD and POD2 (**Table 3**, **Figure 5**).

Discussion

It is important to differentiate ESI approaches for DM patients and non-DM patients. The glucocorticoid used in ESI induces higher-level and longer-lasting hyperglycemia and hypocortisolism in DM patients, compared to non-DM patients. This is also true for steroid injections into the joints of DM patients [5, 6, 10]. These metabolic and hormonal changes, following ESI in DM patients, contribute to postoperative side effects [1]. Reducing hyperglycemic excursion in DM patients exposed to glucocorticoids, therefore, has been recommended [8]. However, few studies have attempted to elucidate specific perioperative glycemic control measures for DM patients during ESI.

According to current results, FPG levels did not change the next day or the 10th day following ESI in the DM group. However, some patients (5 out of 14, 36%) in the DM group demonstrated increased FPG (47.4 mg/dL, 35% elevation) the next day, even with hypoglycemic medications. This elevation of FPG in the FPGUP-DSG group was higher than that in the non-DM group (16 mg/dL, 16%) and FPGUP-NSG group (23 mg/dL, 24%).

For non-DM and DM groups and the FPGUP-NSG group, scores for LBP, leg pain, and ODI improved following ESI. However, none of the clinical scores improved in the FPGUP-DSG group. Although patients with less severe HbA1C and with well-controlled blood glucose were selected as subjects, based on endocrinologist guidance, some (FPGUP-DSG) demonstrated hyperglycemia even with glycemic control with insulin during the ESI perioperative period. This

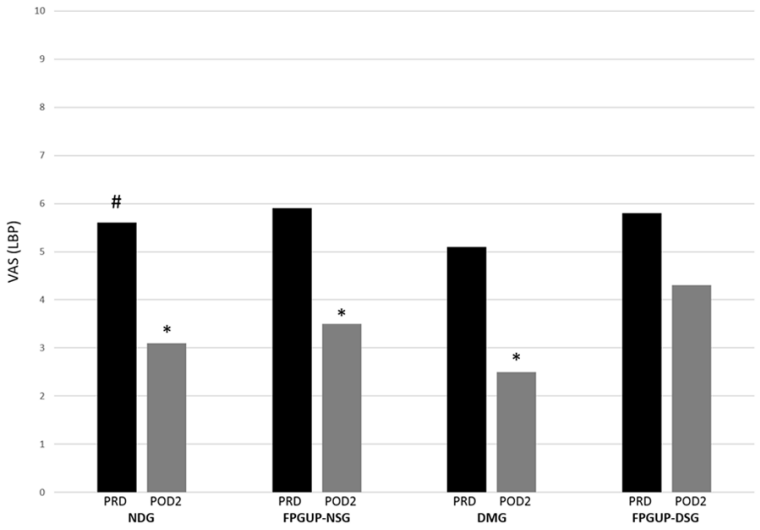

Figure 3. Scores for LBP significantly improved, postoperatively, in non-DM (NDG) and DM (DMG) groups and the FPGUP-NSG group (*), but not in the FPGUP-DSG group. Preoperative score for LBP were significantly greater in the NDG group than the DMG group (#).

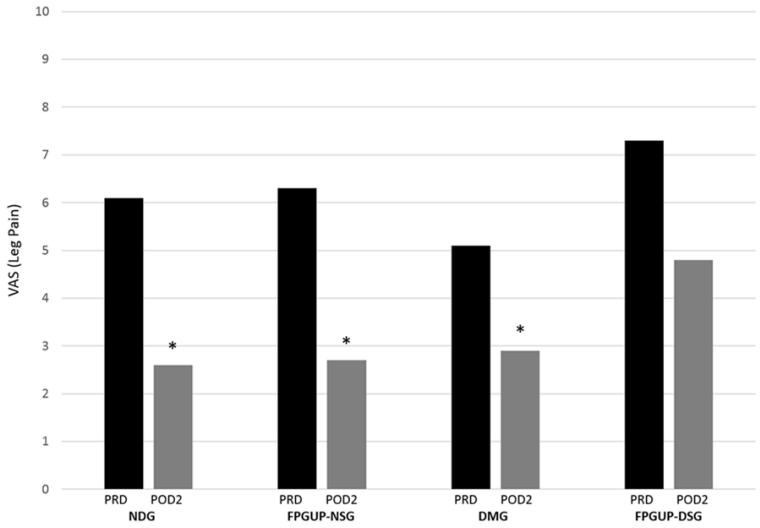

Figure 4. Scores for leg pain significantly improved, postoperatively, in non-DM (NDG) and DM (DMG) groups and the FPGUP-NSG group (*), but not in the FPGUP-DSG group.

suggests that DM patients that do not respond well to perioperative glycemic control might not be good candidates for ESI.

Patients in the FPGUP-DSG group may have suffered from DM for a longer time period with additional factors, such as higher insulin resistance and more possibilities of diabetic neuropathy, compared to the remaining DM group. In addition to patients at risk of failing ESI (depression or any psychiatric condition, uncontrollable opioid use, prior spine surgery, unbearable pain of 10 points on numerical rating scale, DM with increase of HbA1C) [11, 12], DM patients with lower HbA1C (≤8.0% in the current study), if post-ESI hyperglycemia was uncontrolled by perioperative insulin, were added to this group.

In a study by Kim et al. [13], the mean elevation in FPG was 50 mg/dL (39%) from baseline (129 mg/dL) the next day after ESI, using 40 mg of triamcinolone in one group of DM patients (HbA1C, mean 7.15%). The mean elevation was 15 mg/dL (11%) elevation from baseline (131 mg/dL) after ESI, using 20 mg of lowered triamcinolone in another group of DM patients (HbA1C, 7.39%). Thus, it was suggested that blood glucose excursion after ESI could be controlled, even in DM patients, by lowering the dose of corticosteroids or by adding perioperative glycemic control using insulin with maintained doses of corticosteroids.

In a study by Habib et al. [5], lowered serum cortisol levels, following ESI of 80 mg of methylprednisolone (equivalent to 100 mg of prednisolone) [14], did not recover until the 3rd week. Levels were fully restored at the 4th week. In contrast, levels were restored at the 3rd week after ESI of 40 mg of lowered methylprednisolone. Lowered serum cortisol returned to baseline on the 10th day, according to current results. This indicates that post-ESI hypocortisolism was restored in a shorter time period than in previous studies. This might be attributable to the characteristic potential of the nonparticulate steroid, dexamethasone. The lack of differences in restoration times of hypocortisolism in DM, compared to non-DM

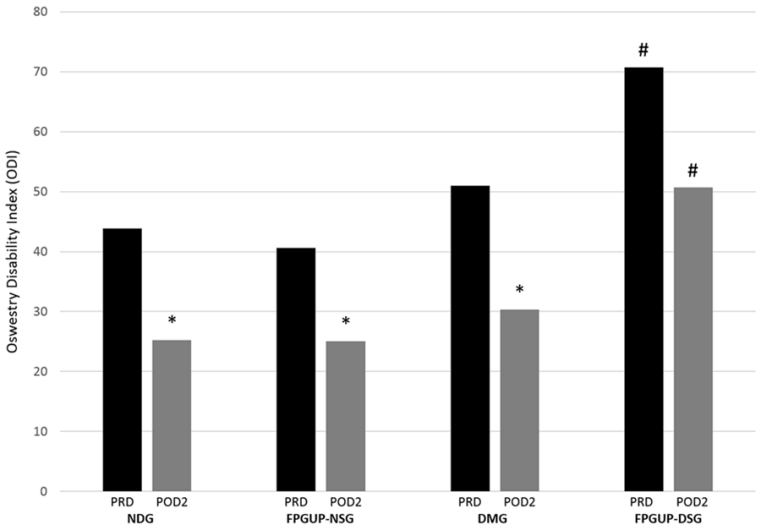

Figure 5. Scores for ODI significantly improved, postoperatively, in non-DM (NDG) and DM (DMG) groups and the FPGUP-NSG group (*), but not in the FPGUP-DSG group. ODI scores, at each time point, were significantly greater (clinically worse) in the FPGUP-DSG group than the FPGUP-NSG group (#).

groups, can be attributed to perioperative glycemic control with insulin for DM patients during ESI.

Dexamethasone has been considered slightly more effective in improving disabilities, but inferior in reducing spinal pain, compared to particulate steroids in patients with acute radiculopathy [15, 16]. However, these therapeutic effects of dexamethasone have been reported to continue for a shorter time period, compared to particulate steroids. Therefore, repeated injections can be performed in more cases [17]. Restoration of hypocortisolism in a shorter time period, in the current study, may correlate with a shorter period of therapeutic effects of dexamethasone.

However, sample sizes for the DM group and subgroups were small. Present results were obtained from limited time points over a short follow-up period. Verification of current results should be conducted in future studies, utilizing more patients over a longer time frame.

Conclusion

Pronounced and prolonged blood glucose excursion and hypocortisolism after ESI in DM patients can be controlled by selecting dexamethasone, instead of a particulate steroid, and adding perioperative glycemic control without reducing corticosteroid doses. However, in DM patients with uncontrolled hyperglycemic excursion with perioperative insulin, clinical symptoms of lumbar spinal stenosis may not improve, even after ESI. DM patients with less-controlled hyperglycemia under perioperative glycemic control might be at risk for failed ESI in terms of clinical effectiveness.

Disclosure of conflict of interest

None.

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