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Randomized Trial

Relationship Between Epidural Steroid Dose and Suppression of Hypothalamus-Pituitary-Adrenal Axis

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Background: The suppression of hypothalamic-pituitary-adrenal (HPA) axis is a common complication associated with epidural steroid injections (ESIs). However, the effect of different doses is unknown.

Objectives: The primary objective was to compare the differences in the duration of HPA suppression following treatment with different doses of ESI; triamcinolone acetate (TA) 40 mg and TA 20 mg. The secondary objectives were to compare the extent of salivary cortisol (SC) reduction, the incidence of adrenal insufficiency (AI), and the differences in a numeric rating scale (NRS) depending on the varying levels of TA dose used for ESI.

Study Design: A double-blind, parallel-group, randomized controlled trial.

Setting: Pain clinics in a university hospital.

Methods: The patients were treated with TA epidurally and divided into 2 groups (T20 and T40) depending on the dose of TA (20 mg and 40 mg). The SC concentration was measured before and after ESI to calculate the duration of HPA axis suppression, the extent of SC concentration reduction, and the SC recovery rate. Additionally, NRS and adrenocorticotropic hormone stimulation tests were used.

Results: Thirty patients were analyzed. The T40 group showed longer HPA suppression (19.7 ± 3.1 days) compared with that of the T20 group (8.0 ± 2.4 days). The recovery rate of the T40 group was lower than that of the T20 group ($P < 0.015$). However, there was no difference in the extent of reduction in SC concentration after ESI, the occurrence of AI, and pain reduction.

Limitations: There were selection bias and no placebo control.

Conclusions: Although the difference in pain relief according to the ESI dose is not significant, the HPA suppression is prolonged with a higher dose than a lower dose, and the recovery is slower. Therefore, the time interval between consecutive ESIs should be adjusted depending on the steroid dose to ameliorate the adverse effects of steroids.

Key words: Adrenal insufficiency, adverse effects, cushing's syndrome, epidural injections, glucocorticoids, optimal dosage, pituitary-adrenal system, salivary cortisol

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Glucocorticoids are potent anti-inflammatory and immunosuppressive hormones with a rapid mechanism of action. However, the potential risks include hypothalamic-pituitary-adrenal (HPA) axis suppression, iatrogenic Cushing's syndrome, adrenal insufficiency (AI), osteoporosis, gastrointestinal problems, hypertension, glaucoma, acne, diabetes mellitus, weight gain, and psychosis (1).

The use of glucocorticoids for the treatment of spine disease has been increasing to avoid hasty surgical interventions. However, patients are exposed to the risks of glucocorticoid-induced complications, suggesting the need for caution, especially, with respect to the optimal dose, frequency, and interval of epidural steroid injection (ESI). Due to a lack of pharmacological information pertaining to epidural steroids, no clear guidelines regarding the optimal dose, frequency, or interval for ESIs are available (2-4).

In this study, we focused on the optimal dosage of glucocorticoids for ESI given the adverse hormonal effects (1). In a previous study, the function of HPA axis in all patients who were treated with triamcinolone acetate (TA) 40 mg as the ESI was suppressed temporarily and was restored after a mean duration of 19.9 ± 6.8 days (5). However, the effect of different doses of glucocorticoid on HPA axis suppression remains unknown.

Several methods have been used to evaluate the function of HPA axis. To evaluate the basal function of HPA axis, early morning levels of blood cortisol or urinary cortisol were measured using a dynamic stimulation test, such as the low-dose adrenocorticotropic hormone (ACTH), at both 30- and 60-min intervals to diagnose AI (6). However, sampling using these diagnostic methods is invasive or cumbersome. In this study, the salivary cortisol (SC) measurement was used to evaluate the HPA function and the ACTH stimulation test due to the convenience in obtaining samples. Further, SC reflects the free fraction of cortisol, a biologically active form (7-9). Analysis of SC in 174 patients revealed that the mean intra-assay coefficients of variation (CVs) were below 2.5%, and the mean inter-assay CVs were below 2.8% (10). The ACTH stimulation test also enables SC measurement (11).

We hypothesized that higher amounts of TA for ESI prolong HPA suppression. The primary objective of the study was to compare the differences in the duration of HPA suppression following treatment with different doses of ESI (TA 40 mg and TA 20 mg). The secondary objectives were to compare the extent of SC reduction, the incidence of AI, and the differences in numeric rating scale (NRS) depending on the TA dose.

Methods

Study Design

This study was a parallel-group, double-blind, randomized controlled trial, which was registered with the Clinical Research Information Services (CRiS) of the Republic of Korea (KCT0004778). The Institutional Review Board of the Catholic University of Korea approved the study protocols (SC12OISI0150). All patients provided written informed consent to participate in the study.

Patients

The inclusion criteria were: American Society of Anesthesiologists Physical Status 1 or 2 classification; aged above 40 years; men and postmenopausal women; patients diagnosed with lumbar herniation of nucleus pulposus (HNP) or spinal stenosis based on the nature of pain, pain location, neurogenic intermittent claudication, factors exacerbating or attenuating pain, and signs such as a positive straight leg raise, sensory, motor, and deep tendon reflexes, as well as magnetic resonance imaging (MRI) findings: disc bulging, protrusion, extrusion, and sequestration in HNP or spinal canal narrowing in spinal stenosis associated with corresponding symptoms; and patients who were matched for ESI.

The exclusion criteria were: absolute contraindication for ESI (bleeding tendency and infection at the procedure site); treatment with glucocorticoids during recent 3 months; contraindication for glucocorticoids, due to allergy to steroid agents, pregnancy, or endocrine diseases; sleep disturbances; treatment with herbal medicine or contraceptives; severe stress during the preceding month; and alcohol or food intake 12 h or 1 h before sampling, respectively. Patients were enrolled at a university hospital from November 2017 to February 2018.

Intervention

All patients received a single injection of 20 mg or 40 mg TA epidurally under C-arm guidance for ESI. A contrast medium was also injected to recognize an intravascular injection of TA, which affected drug pharmacokinetics. None of the patients received additional ESIs during the follow-up period of 28 days.

Outcomes

The primary outcome of this study was the duration of HPA axis suppression following injection with different doses of ESI (TA 40 mg and TA 20 mg). To measure the duration of HPA axis suppression, early morning levels of SC were determined. The SC concentration was affected by factors such as sampling time, age, season, and exposure to sex hormones (12,13). Generally, in healthy individuals manifesting regular sleep patterns, the peak SC concentration is observed in

the morning (0800 h) and an SC nadir at late night (2300 h) (12,14). To minimize the confounding effects of the circadian rhythm of SC, the SC samples were obtained at the same time (0800~0900 h) and in the same season (winter in Korea). In addition, postmenopausal women were selected to minimize the effect of sex hormones. Similar age groups (above 40 years) were selected. The SC data for the measurement of HPA axis suppression were collected before ESI (D0), and on days 1 (D1), 7 (D7), 14 (D14), 21 (D21), and 28 (D28) after ESI. The duration of HPA axis suppression was calculated via interpolation, i.e., construction of new data points within the range of a discrete set of known data points (D0, D1, D7, D14, D21, and D28). The criteria for normalization were above 1.0 μg/dL for early morning SC levels during the follow-up periods (15). Saliva was obtained from the patients using a commercially available cotton sampling device, Salivette (Salimetrics, State College, PA). Patients were instructed to rinse their mouth thoroughly with water 10 min before sample collection. They stored their saliva sample in a freezer compartment. Salivary samples were frozen at or below -20°C within 4 h after collection (16). The patients revisited the hospital on D28 with their saliva samples in a cooler. The SC concentration was measured by ELISA using the VersaMax ELISA Microplate Reader (Molecular Devices, Sunnyvale, CA).

Secondary outcomes included the extent of SC reduction after ESI, differences in NRS (0, no pain; 10, the worst pain imaginable) between D0 and D28, the results of ACTH stimulation test, and SC concentration trends after ESI. The extent of reduction (%) of SC concentration after ESI was defined by the following equation:

$$SC\ conc.reduction\ (\%) = \frac{SC(D0) - SC(D1)}{SC(D0)} \times 100$$

The ACTH stimulation test was conducted on D28 in the morning. The SC concentration was measured 3 times; SC_0 (before the parenteral administration of 250 μg cosyntropin) (17), SC_{30} (after 30 min), and SC_{60} (after 60 min). AI was diagnosed based on a maximal SC concentration (SC_0, SC_{30}, and SC_{60}) after ACTH stimulation ranging between 0.018 and 0.551μg/dL (11).

Sample Size

Based on a previous study (5), we estimated that a sample size of 15 patients in each group was adequate to detect a 7-day difference in the mean duration of HPA suppression after exposure to the 2 different doses of ESI (TA 20 mg and TA 40 mg). Assuming a confidence level of 95% and a study power of 80%, the type 1 error was set at 5%. A *P* value was considered significant at a level of < 0.05. To account for dropouts, we enrolled 19 patients in each group.

Randomization

A co-author (HJH) enrolled patients, generated the random allocation sequence, and assigned patients to interventions. A simple randomization was used and the patients were randomly assigned to 2 equal groups: T20 and T40. The randomization numbers generated using a computer were placed in sealed envelopes (opaque, not resealable) and opened before the procedure. Each subject was assigned a unique identification number for the duration of the study.

Blinding

Patients and a clinician (HSM) responsible for treatment were blinded to the TA dose injected. The blinding was removed on D28. The steroid mixture was prepared in advance by a single safety assessor before the intervention and used by the treating clinician (HSM) during the procedure. The mixture of TA 20 mg, 2% mepivacaine 1 mL, and normal saline 3.5 mL was used for active control treatment. The mixture of TA 40 mg, 2% mepivacaine 1 mL, and normal saline 3 mL was used for experimental treatment. For blinding, both mixtures were prepared and were visually indistinguishable.

Statistical Analysis

The R language version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and T&F program ver. 2.9 (YooJinBioSoft, Korea) were used for all statistical analyses. Data were expressed as mean ± standard deviation (SD) for continuous variables, including age, body mass index (BMI), NRS, and serum ACTH. Mann-Whitney test was used to compare the mean differences between patient groups defined by steroid concentrations or AI. Data for categorical variables were expressed as sample number and percentage, n (%). Fisher's exact test was used to determine the association between patient groups and other categorical variables, such as diagnosis, gender, history of steroid exposure, and abnormal serum ACTH. False discovery rate (FDR) was adopted for multiple test correction.

Univariable and multivariable binary logistic regression analyses were performed to analyze the effect of each clinical factor measured on the incidence of AI. A linear mixed-effects (LME) model was generated to analyze the fixed effects of time and other baseline

covariates including age, gender, and BMI on SC, where time and each variable were used as the fixed-effect covariates with a random effect of intercept and slope of time for patients. The slope of SC derived from the mixed-effects model was compared between patient groups defined by steroid levels or AI occurrence using the Mann-Whitney U test. Lattice plots were generated to compare the temporal trend in the response of each patient. $P < 0.05$ was considered statistically significant.

Results

We enrolled 38 eligible patients who signed the informed consent to participate in the study. The patients were randomly assigned into 2 groups to receive the allocated intervention. Eight patients were excluded from the study. Two patients in the T20 group and one subject in the T40 group were lost to follow-up. The data of 5 patients (2 in the T20 and 3 in the T40 group) could not be analyzed due to insufficient salivary sample (Fig. 1). The recruitment period was 28 days. There was no difference in baseline data between T20 and T40 groups (Table 1).

Duration of HPA Axis Suppression after ESIs

The duration of HPA axis suppression was defined as the time from ESI to reach SC 0.1 μg/dL, which is the minimal level in the normal range of SC (0.1~1.0 μg/dL) (15), and was calculated via linear interpolation or extrapolation. A linear interpolation was used when the patient's SC reached 0.1 μg/dL within 28 days. However, when SC did not reach 0.1 μg/dL, a linear extrapolation was applied. Three patients (2 in the T20 group and one in the T40 group) whose SC (D28) was less than SC (D21) were assigned a missing value because the linear extrapolation method failed. As a result, the duration of HPA axis suppression in the T40 group (19.7 ± 3.1 days) was significantly longer than in the T20 group (8.0 ± 2.4 days) (Fig. 2).

The Extent of Reduction in SC Concentration after ESI

The extent of reduction (%) of SC concentration after ESI was 84.5 ± 4.4% in the T20 group and 87.3 ± 3.4% in the T40 group. There was no statistical difference in SC concentration reduction (%) between the 2 groups ($P = 0.74$) (Fig. 3). Eight of the 30 patients were diagnosed with AI (Table 2). However, the difference in AI incidence between both groups was not significant (Table 3), and there was no patient with ACTH insufficiency (Table 2).

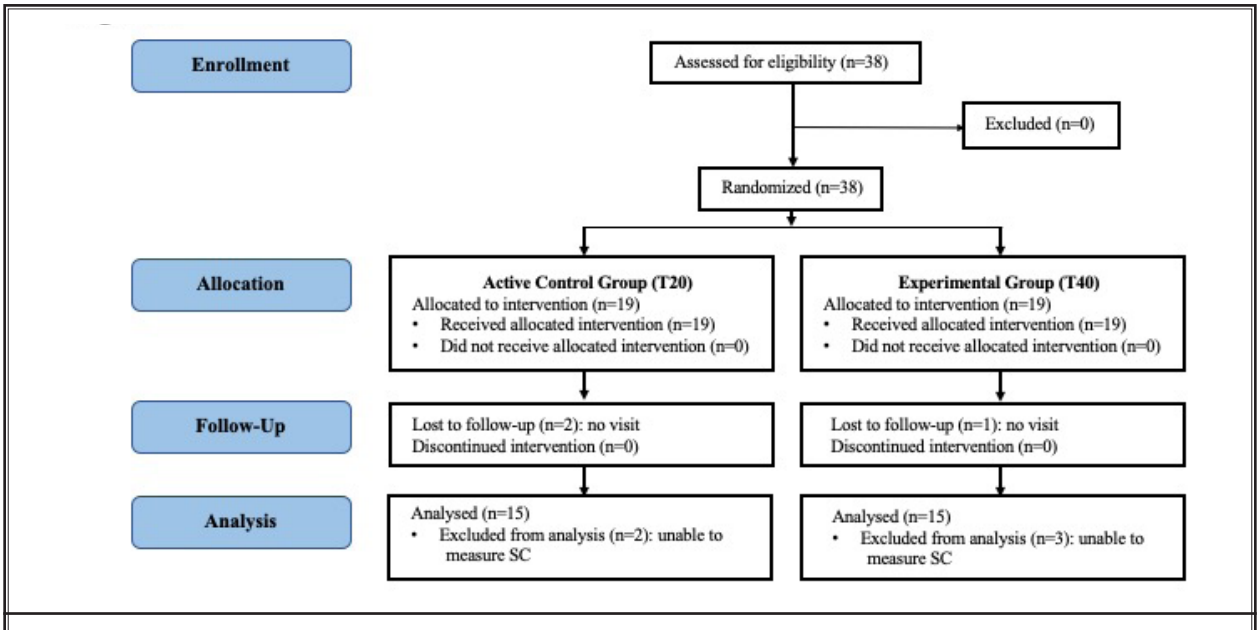

Fig. 1. *Flow diagram outlining the study protocol.*

T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally; SC: salivary cortisol.

Table 1. *Demographic characteristics of variables.*

Variables		n (%)	Range	T20 group	T40 group	*P* value
Sample No. (%)		30 (100)		15 (50)	15 (50)	
Diagnosis		30 (100)				0.44
	L-HNP	18 (60.0)		7 (46.7)	11 (73.3)	
	C-HNP	7 (23.3)		4 (26.7)	3 (20.0)	
	Spinal stenosis	3 (10.0)		2 (13.3)	1 (6.7)	
	FBSS	2 (6.7)		2 (13.3)	0 (0)	
Age, years		30 (100)	55.7 ± 13.7	55.5 ± 14.6	56.0 ± 13.2	0.97
Gender		30 (100)				0.71
	M	12 (40.0)		7 (46.7)	5 (33.3)	
	F	18 (60.0)		8 (53.5)	10 (66.7)	
BMI		30 (100)	24.1 ± 3.1	23.9 ± 2.7	24.3 ± 3.5	0.79
Steroid exposure history		30 (100)				0.33
	naïve	5 (16.7)		4 (26.7)	1 (6.7)	
	Non-naïve	25 (83.3)		11 (73.3)	14 (93.3)	
NRS (D0)		30 (100)	5.4 ± 1.0	5.3 ± 0.9	5.5 ± 1.2	0.55
NRS (D28)		30 (100)	2.6 ± 1.1	2.7 ± 1.1	2.6 ± 1.2	> 0.99
NRSdiff (D0-D28)		30 (100)	2.8 ± 1.0	2.6 ± 0.8	2.9 ± 1.2	0.72
Serum ACTH (D28)		30 (100)	35.3 ± 17.7	30.4 ± 11.4	40.3 ± 21.6	0.30
Abnormality of serum ACTH (D28)		30 (100)				0.60
	Normal	26 (86.7)		14 (93.3)	12 (80.0)	
	Abnormal	4 (13.3)		1 (6.7)	3 (20.0)	

T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally; L-HNP: lumbar herniated nucleus pulposus; C-HNP: cervical herniated nucleus pulposus; FBSS: failed back surgery syndrome; BMI: body mass index; NRS (D0): numeric rating scale on day 0; NRS (D28): numeric rating scale on day 28; NRSdiff(D0-D28): NRS difference between day 0 and day 28; and ACTH: adrenocorticotropic hormone.

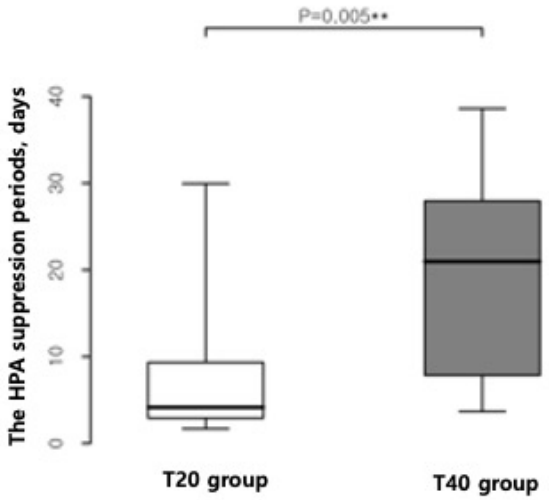

Fig. 2. ***Comparison of HPA suppression duration between the T20 and T40 groups.***

The duration of HPA axis suppression in the T40 group (19.7 ± 3.1 days) was significantly longer than in the T20 group (8.0 ± 2.4 days). HPA: hypothalamus-pituitary-adrenal; T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally. *P* value * < 0.05, *P* value ** < 0.01

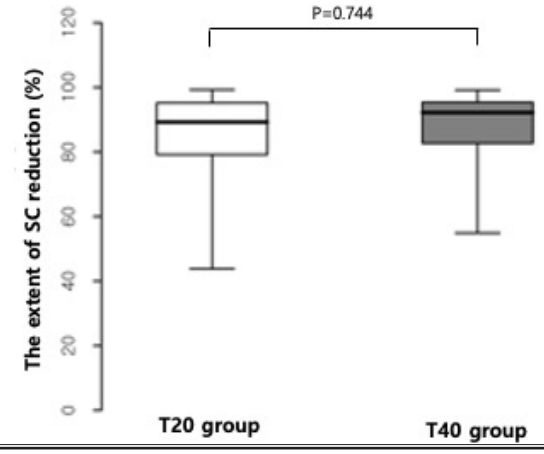

Fig. 3. *Comparison of mean differences in SC concentration reduction (%) between the T20 and T40 groups.*

There was no difference in the extent of SC reduction (%) on D1 in both groups. SC: salivary cortisol; T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally; D1: day 1 after epidural steroid injection.

Table 2. *Results of ACTH stimulation test.*

Patients	Group	Serum ACTH (D28) (6-56.7 pg/mL)	SC_0µg/dL	SC_{30}g/dL	SC_{60}µg/dL	Diagnosis of AI (0.018-0.551 µg/dL)
1	T40	40.82	0.302	0.580	0.923	Normal
3	T40	46.73	0.206	0.198	0.326	AI
4	T20	26.04	0.459	0.570	0.480	Normal
5	T40	40.39	0.111	0.453	0.665	Normal
6	T20	18.34	0.081	0.507	0.607	Normal
7	T20	26.63	0.284	0.137	0.290	AI
9	T20	46.16	0.309	0.216	0.407	AI
10	T20	37.52	0.176	0.507	0.761	Normal
11	T40	16.22	0.155	1.371	0.170	Normal
12	T20	26.63	0.343	0.855	1.302	Normal
13	T40	*82.55	0.229	0.211	0.165	AI
14	T40	37.21	0.252	0.547	0.800	Normal
15	T20	*56.79	0.076	0.435	0.933	Normal
16	T20	34.56	0.364	1.431	1.971	Normal
17	T40	52.38	0.125	0.403	0.607	Normal
18	T20	22.42	0.346	0.513	1.122	Normal
19	T40	*67.32	0.050	0.344	0.647	Normal
20	T20	20.44	0.007	1.209	1.316	Normal
21	T20	21.71	0.265	0.480	0.790	Normal
25	T20	19.84	0.157	0.927	0.983	Normal
26	T40	24.37	0.132	0.308	0.380	AI
27	T40	52.77	0.014	0.110	0.190	AI
28	T40	*68.60	0.294	0.604	0.505	Normal
29	T40	23.12	0.064	0.413	0.721	Normal
31	T40	8.30	0.133	0.531	0.849	Normal
32	T20	45.92	0.107	0.565	0.967	Normal
33	T20	25.15	0.234	0.361	0.683	Normal
35	T40	18.73	0.110	0.175	0.268	AI
36	T20	28.06	0.279	0.760	0.700	Normal
37	T40	24.55	0.064	0.159	0.141	AI

The SC concentration was measured 3 times; SC_0 (before the parenteral administration of 250 µg cosyntropin), SC_{30} (after 30 minutes), and SC_{60} (after 60 minutes). AI was diagnosed by the maximal SC concentration (SC_0, SC_{30}, andSC_{60}) after ACTH stimulation ranging between 0.018 and 0.551 µg/dL. T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally; AI: adrenal insufficiency. * abnormal serum ACTH concentration.

SC Concentration after ESI in LME Model

The SC concentration trend after ESI in each patient was analyzed using an LME model (Fig. 4). The SC concentration trended upward with time except in case 15 (T20 group), case 20 (T20 group), and case 27 (T40 group). AI was observed only in case 27. Time was the only variable that significantly affected the SC trend with a fixed effect after adjustment for the random effects and baseline variables ($P < 0.001$), suggesting that SC increased significantly over time (ß = 0.005) (Table 4).

Table 3. *Incidence of AI.*

Subgroup	n (%)	T20 group	T40 group	*P* value	OR (95% CIs)
Sample No (%)	30 (100)	15 (50)	15 (50)		
Non-AI	22 (73.3)	13 (86.7)	9 (60.0)	0.22	1
AI	8 (26.7)	2 (13.3)	6 (40.0)		4.33 (0.71-26.53)

There was no statistical difference in OR of AI incidence between the 2 groups. *P* value was computed using Fisher's exact test. AI: adrenal insufficiency; T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally; OR: odds ratio.

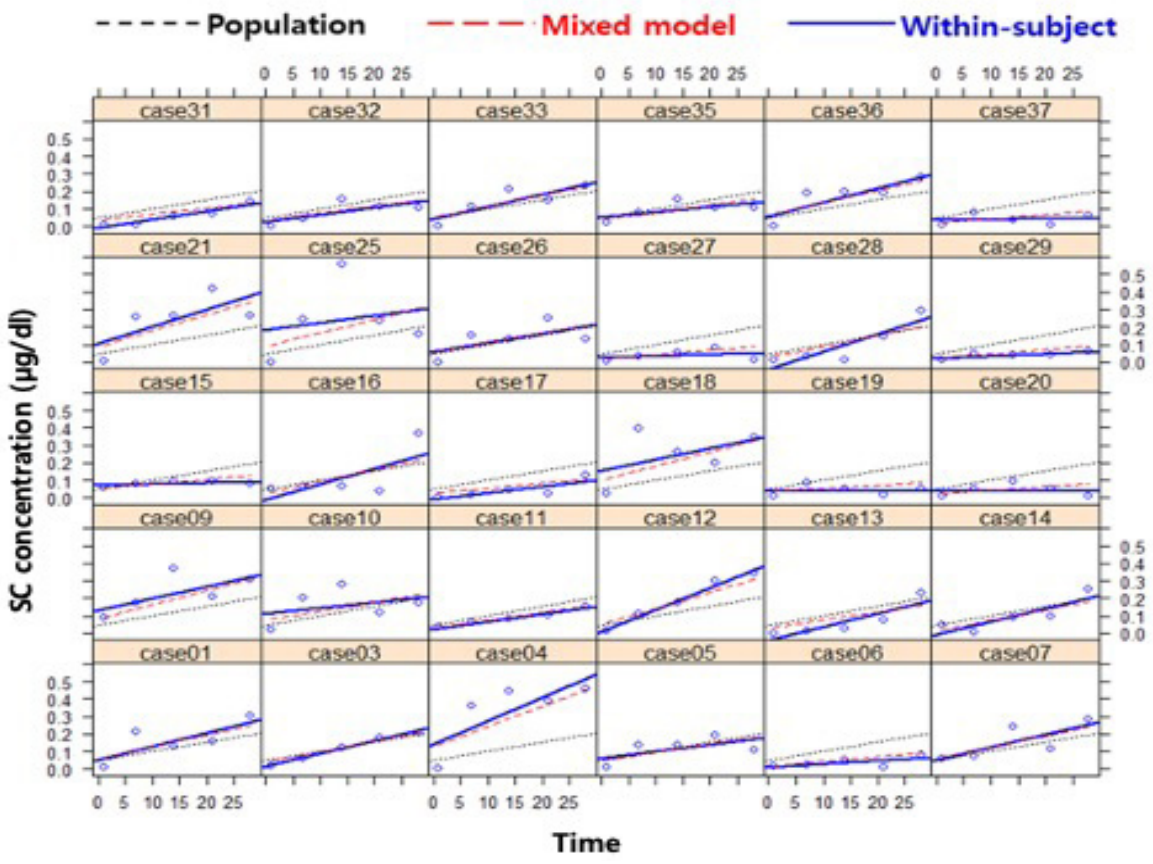

Fig. 4. *Comparison of SC concentration trends in each patient.*

Black dotted line: linear regression line estimated using population; red dashed line: fitted line estimated using a mixed-effects model; blue solid line: linear regression line estimated using subject-specific data; blue point circle: SC measured at the corresponding time; X-axis: time in days; SC: salivary cortisol.

Table 4. *Fixed effects of time and covariates.*

	ß	Standard Error	*P* value
(intercept)	0.126	0.089	0.17
Age	-0.000	0.001	0.83
Sex	-0.012	0.026	0.65
BMI	-0.002	0.005	0.66
Time	0.005	0.001	< 0.001

ß: coefficient of fixed effect; Standard Error: standard error of beta.

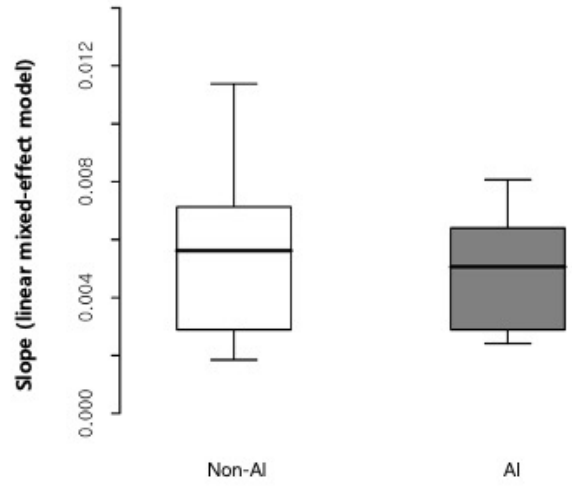

Fig. 6. Comparison of mean differences in slope (LME model) between non-AI and AI patients expressed as 1/4Q, median, 3/4Q.

LME: linear mixed-effects model; AI: adrenal insufficiency; Q: quartile; *P* value was computed using the Mann-Whitney U test.

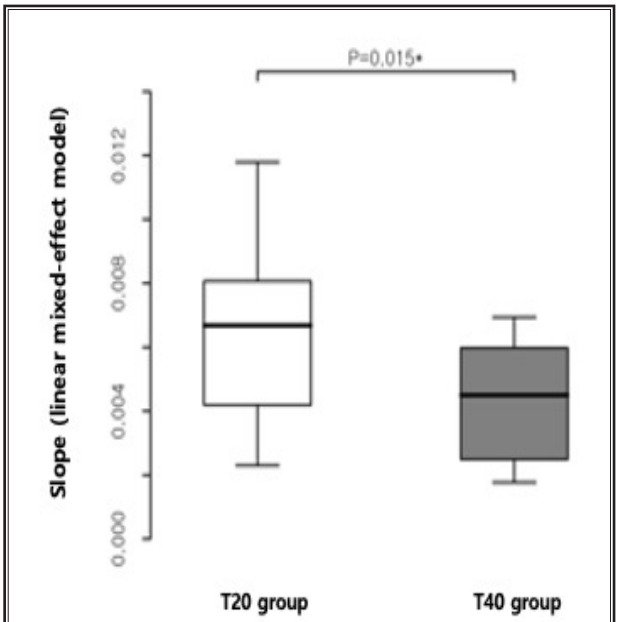

Fig. 5. *Comparison of mean differences in slope (LME model) between T20 and T40 groups expressed as 1/4Q, median, 3/4Q.*

LME: linear mixed-effects model; T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally; Q: quartile; P value * < 0.05, which was computed using the Mann-Whitney U test.

Difference in SC Trend of Each Patient Group in the LME Model

The slope of T20 group (0.00647 ± 0.00069) was more inclined than that of T40 group (0.00431 ± 0.00043) ($P < 0.015$) (Fig. 5). The slope refers to the rate of SC increase calculated for each individual based on the LME model, i.e., the SC recovery rate after ESI using a smaller dose (T20) was faster than that of a larger dose (T40). However, there was no significant difference between non-AI (n = 22, 0.00554 ± 0.00056) and AI patients (n = 8, 0.00497 ± 0.00069) ($P = 0.565$) (Fig. 6).

The Mean SC Difference between T20 and T40 Groups at each Time

In general, after ESI, the SC decreases dramatically until D1 regardless of dose (Fig. 7). It recovers gradually after D1 and earlier within the T20 group than in the T40 group (Table 5).

Discussion

The T40 group had a longer HPA suppression compared with the T20 group, and the recovery rate of the T40 group was lower than that of the T20 group. However, there was no difference in the extent of reduction in SC concentration after ESI, the occurrence of AI, and pain reduction.

The glucocorticoid dose for ESI usually depends on the physician's experience or on the guidelines recommended for other steroidal injections, such as intraarticular steroids (18,19). In Korea, most of the pain physicians use dexamethasone or TA for ESI. In the case of TA, 21.3 ± 12.0 mg of TA for interlaminar ESI and 18.8 ± 9.8 mg of TA for transforaminal ESI was used empirically (20). Kang S. et al (21) suggested that a minimally effective dose for ESI was TA 10 mg. Ahadian FM et al (22) recommended that the optimal dose of epidural dexamethasone was lower than 4 mg. Although inves-

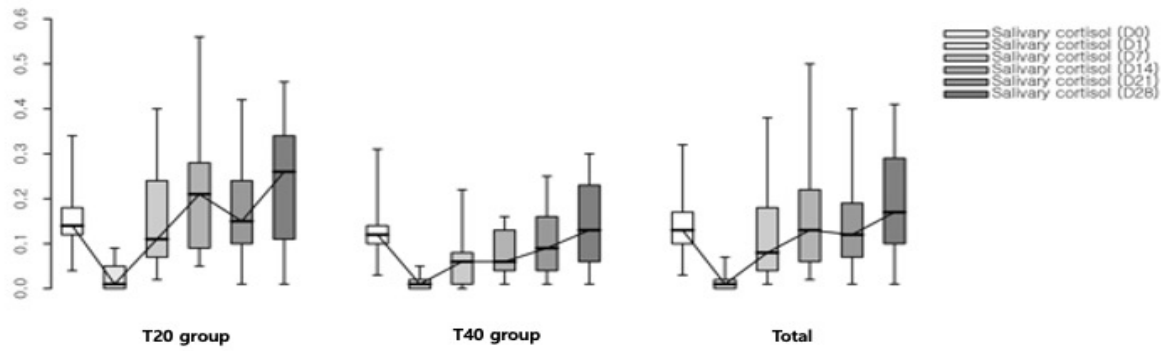

Fig. 7. *Temporal variation in SC of different patient groups.*

SC: salivary cortisol; T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally; D1: day.

Table 5. *Temporal variation in mean SC levels of T20 and T40 groups.*

Variables	T20 group	T40 group	*P* value	*P* value adjusted by FDR
SC (D0)	0.157 ± 0.020	0.126 ± 0.017	0.148	0.178
SC (D1)	0.024 ± 0.007	0.013 ± 0.003	0.519	0.519
SC (D7)	0.159 ± 0.030	0.068 ± 0.016	0.017*	0.051
SC (D14)	0.231 ± 0.037	0.079 ± 0.012	< 0.001**	0.001**
SC (D21)	0.176 ± 0.031	0.103 ± 0.018	0.059	0.093
SC (D28)	0.232 ± 0.033	0.150 ± 0.023	0.062	0.093

Variables are expressed as Mean ± SE (standard error). The difference in mean SC between 2 groups was analyzed using a 2-sample T-test at each time, and the *P* value was adjusted via a multiple test correction of FDR. SC: salivary cortisol; T20 group: patient group treated with triamcinolone acetate 20 mg epidurally; T40 group: patient group treated with triamcinolone acetate 40 mg epidurally; D: day; FDR: false discovery rate. *P* value * < 0.05, *P* value ** < 0.01

tigations with different types of glucocorticoids concluded that a small dose was adequate for appropriate pain control, they considered only the effectiveness of ESI. In this study, a high dose of glucocorticoids (TA 40 mg) for ESI was not superior to a low dose of glucocorticoid (TA 20 mg) in efficacy. Although doses below TA 20 mg were not considered in this study, the smaller the dose, the safer it was.

The interval of ESI is also decided empirically (minimum 2 to 3 weeks) (20). To determine the optimal interval of ESI, the risk-to-benefit ratio should be considered. The HPA suppression period is an important factor contributing to attenuation of the risk. The HPA suppression period in the T20 group (8.0 ± 2.4 days) was significantly shorter than in the T40 group (19.7 ± 3.1 days), which was associated with the recovery rate of SC (Fig. 5). Therefore, for safety reasons, the higher the dose of ESI, the longer the injection interval should be. In theory, when 20 mg of TA is injected, a conservative minimum interval of 10 days is required, and when 40 mg of TA is injected, a minimum of 23 days is required. However, whether the repeated ESIs during such intervals actually affect the HPA suppression requires further studies.

In this study, the occurrence of AI was evaluated because it is one of the severe hormonal complications associated with ESI. Although there was no difference between T20 and T40 groups, AI was detected in 8 of 30 patients (26.7%), which was considerably higher than expected. The prevalence of secondary AI is very rare, ranging between 150 and 280/million (0.00015%-0.00028%) (23). The wide range in incidence may be attributed to appropriate timing of the examination, the reliability of the examination method, and the underes-

timated secondary AI incidence. There are no standard criteria determining the timing of the examination. In this study, the ACTH stimulation test was conducted on D28, and whether or not the adrenal function remained unchanged at the time cannot be established. Therefore, an additional test to confirm AI is needed. The golden standard for evaluation of AI is the ACTH stimulation test based on serum cortisol measurement. The ACTH stimulation test (250 μg of cosyntropin) for primary AI shows a diagnostic sensitivity of 92% (95% confidence interval, 81-97%) (24). However, its sensitivity in adults for secondary AI was poor, with positive likelihood ratios of 9.1 (with 250 μg of cosyntropin) and 5.9 (with 1 μg of cosyntropin) (24). We conducted the ACTH stimulation test based on SC measurements instead of serum cortisol to improve compliance. The ACTH stimulation test using SC measurement is accurate and noninvasive, reflecting the levels of free cortisol as opposed to serum cortisol (7,11).

The study has several limitations. Selection bias was the major potential limitation. During the screening session, the baseline adrenal function of patients was not fully evaluated. Although the incidence of AI was not the primary purpose of the study, it represents a potential selection bias affecting the study results. However, AI is known to be a very rare disease and unlikely to occur accidently. Instead, the authors evaluated the patients' medical history and performed careful physical examinations during the screening sessions. Second, there was no placebo control and the dosage of TA was not determined according to the body weight. Clinically, during ESI, the steroid dosage is not recommended according to body weight. However, the drug metabolism may vary by body weight pharmacologically. Third, the study did not perform an additional follow-up of AI patients. Although none of the eight AI patients manifested any symptoms related to AI, additional tests of adrenal function including the secondary ACTH stimulation test are required for accurate diagnosis of AI. In future studies, fewer levels of steroids should be used to determine the optimal dose of ESI. It is also necessary to analyze the differences in HPA suppression duration depending on the type of steroid used.

Conclusion

The difference in pain relief according to the dose of ESI was not significant. However, the HPA suppression was longer at a high dose than at a low dose, and its recovery was slower. Therefore, the time interval between consecutive ESIs should be adjusted depending on the steroid dose to ameliorate the adverse effects of steroids.

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