Pain Physician 2013; 16:557-568 • ISSN 1533-3159

Prospective Evaluation

Effects of Two Different Doses of Epidural Steroid on Blood Glucose Levels and Pain Control in Patients with Diabetes Mellitus

Won Ho Kim, MD[1], Woo Seog Sim, MD, PhD[1], Byung Seop Shin, MD, PhD[1], Chul Joong Lee, MD, PhD[2], Hyun Seung Jin, MD[1], Jin Young Lee, MD[1], Hee Jin Roe, MD[1], Chung Su Kim, MD, PhD[1], and Sangmin M. Lee, MD, PhD[1]

From: [1]Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[2]Zeropain Pain Management Clinic, Seoul, Republic of Korea

Address Correspondence:
Woo Seog Sim, MD, PhD
Department of Anesthesiology and Pain Medicine
Samsung Medical Center
Sungkyunkwan University School of Medicine
50 Irwon-Dong, Gangnam-Gu, Seoul 135-710
Republic of Korea
E-mail: wooseogsim.ane@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might post a conflict of interest in connection with the submitted manuscript.

Manuscript received: 03-30-2013
Revised manuscript received: 05-19-2013
Accepted for publication: 05-21-2013

Free full manuscript: www.painphysicianjournal.com

Background: A high incidence of diabetes mellitus has been reported among patients diagnosed with lumbar degenerative spinal diseases. Although epidural steroid injections are known to increase the postprocedure blood glucose level, it has not been investigated whether a lower steroid dose can reduce blood glucose excursions and still be effective in controlling patients' subjective pain.

Objective: We compared the effects of 2 common doses of triamcinolone administered via epidural steroid injections on blood glucose levels and pain control in patients with diabetes mellitus to determine an adequate epidural steroid dose.

Study Design: A prospective observational study.

Methods: One hundred patients with diabetes mellitus were enrolled. They received lumbar transforaminal, lumbar interlaminar, or caudal epidural triamcinolone for radiculopathy, spinal stenosis, or failed back surgery syndrome. After the type of procedure was clinically determined, the doses of triamcinolone given were randomly chosen, either 40 mg (Group 40) or 20 mg (Group 20). The patients were asked to measure their finger stick blood glucose level twice daily (fasting and postprandial) for 3 days before the injection, on the day of the injection, for 7 days after the injection, and at 14 days after the injection. They also kept a blood glucose diary. Employment status and clinical outcome were evaluated at 8 weeks after the procedure.

Results: There were significant increases in fasting blood glucose (FBG) level on postprocedure day (PPD) #1 to PPD #3 in Group 40, but on PPD #1 in Group 20. Moreover, there was a significant difference in FBG between groups on PPD #1 and PPD #2 (FBG on PPD #1: 179 [51]) mg/dL in Group 40 versus 146 [50] mg/dL in Group 20, $P < 0.001$]. Postprandial blood glucose (PBG) level was significantly elevated in both groups from PPD #0 to PPD #3. Notably, the increase in PBG was significantly greater in Group 40 than Group 20 on PPD #0 and #1 (PBG on PPD #0: 288 [57] mg/dL versus 242 [94] mg/dL in Groups 40 and 20, respectively, $P = 0.004$). The numeric rating scale for pain reported by the patients decreased for 2 weeks after treatment with no difference between groups. Employment status and clinical outcome was not different between groups.

Limitations: The patients who chose to participate in this study may be a cohort of well-controlled patients with diabetes mellitus. The type of procedure performed was determined by a clinical decision and not randomized. The different routes of administration and diagnosis of failed back surgery syndrome can result in different levels of systemic absorption, thereby influencing the degree and duration of hyperglycemia. In patients with FBSS, the epidural space may be destructed by surgery and adhesive changes in epidural space could be extensive. Therefore, we thought that the absorption of epidural space in these patients would be incomplete or slow compared with those without FBSS.

Conclusion: Epidural steroid injections were associated with statistically significant elevations in PBG in patients with diabetes for up to 4 days after the procedure. The higher dose of triamcinolone increased FBG and PBG greater than a lower dose did without affecting pain control, employment status, or clinical outcome. Thus, with respect to glucose and pain control, 20 mg of triamcinolone appears to be recommended rather than 40 mg in patients with diabetes.

Clinical Trials registration : NCT01435707

Key words: Epidural steroid injection, low back pain, diabetes, blood glucose

Pain Physician 2013; 16:557-568

The prevalence of lumbar degenerative spinal diseases continues to increase (1). The prevalence of diabetes mellitus (DM) is also on the rise, particularly in the elderly (2). A high incidence of DM has been reported among patients diagnosed with spinal stenosis (3), which was greater than expected compared to an age-matched general population.

Epidural steroid injections (ESI) have become a common treatment modality for degenerative lumbar spinal stenosis (4) or radiculitis secondary to intervertebral disc herniation (5-9). Injections can be performed via interlaminar (7), transforaminal (8), or caudal (6,9) approaches depending on the presenting symptoms and the preference of the clinician. Historically, the administration of steroids has been controversial in those with insulin-dependent or independent DM. Several studies have evaluated the impact of ESI on diabetic patients regarding postinjection blood glucose level (10-12), reporting a significant elevation in blood glucose level for 2 days or up to 7 days according to the kinds of steroid. However, the sample sizes of these studies were very small, the degree of diabetic control was not considered, and the effects on fasting and postprandial blood glucose were not evaluated separately. In addition, these studies simply reported the degree of blood glucose elevations, thus they did not provide any clinical information that could help determine epidural steroid dose in patients with DM or about how to manage steroid-induced hyperglycemia. Since a previous study has reported that an epidural dose of at least 10 mg of triamcinolone is sufficient to provide pain relief compared with higher doses (13), we hypothesized that a lower dose of epidural steroid may reduce the degree of elevation in blood glucose level in patients with DM without decreasing the effect of ESI.

Therefore, we designed a prospective observational study to evaluate the effects of 2 commonly used doses of ESI on blood glucose levels in patients with DM in a cohort with a sample size determined by a power analysis. We also measured subjective pain levels based on a numerical rating scale, as well as employment status and clinical outcome to compare the efficacy of the 2 doses to confirm whether a lower dose is as effective as a higher one.

Methods

This single-center, prospective, observational study was carried out at a university hospital from September 2011 through March 2013. After approval by our Institutional Review Board (2011-08-058) and registration at www.clinicaltrials.org (NCT01435707), those who underwent ESI in the pain management center were assessed for eligibility for our study. All patients provided written informed consent. We prospectively enrolled patients who met inclusion criteria, which included an age $\geq$ 20 years, patients undergoing ESI due to lumbar spinal stenosis or lumbar radiculopathy with symptoms for a period of at least 3 months, and those with a diagnosis of Type I or II DM currently on active therapy and with a record of a hemoglobin A1c level obtained within a month before enrollment.

We excluded patients with severe cardiopulmonary or brain disease; active infection; a history of anaphylactic reaction to contrast medium, anesthetic, or steroids; pregnancy; uncontrolled diabetes with complications; and ongoing anticoagulation therapy. We also excluded those who had undergone ESI within the preceding month or peripheral corticosteroid injection within the preceding 2 weeks. Symptomatic spinal stenosis and radiculopathy were confirmed by magnetic resonance imaging or computed tomography and a standard spine exam.

The procedure was determined by a clinical decision (Fig. 1). Caudal epidural or lumbosacral transforaminal injection was performed for radiculopathy caused by herniated disc or foraminal stenosis. Caudal epidural or lumbosacral transforaminal or lumbar interlaminar injection was performed for spinal stenosis with radiculopathy. Lumbosacral transforaminal injection was performed for failed back surgery syndrome. Thereafter, the patients were assigned to either Group 40 or Group 20 according to their epidural triamcinolone dose of 40 mg or 20 mg, regardless of the procedure performed. Randomization was performed by an internet-based computer program which generated random numbers (www.randomizer.org). The procedure room clinical fellow prepared the drugs according to the random number and the physicians performing the procedure did not know the dosage of triamcinolone.

Outcome Measures

The primary outcome measured was blood glucose recordings from a glucometer distributed by our pain management center. All patients were provided with a blood glucose diary and a glucometer (Accu-Chek Performa, Roche Diagnostics LTD, Mannheim, Germany) to monitor blood glucose level, as well as education regarding its use. Patients were asked to measure their

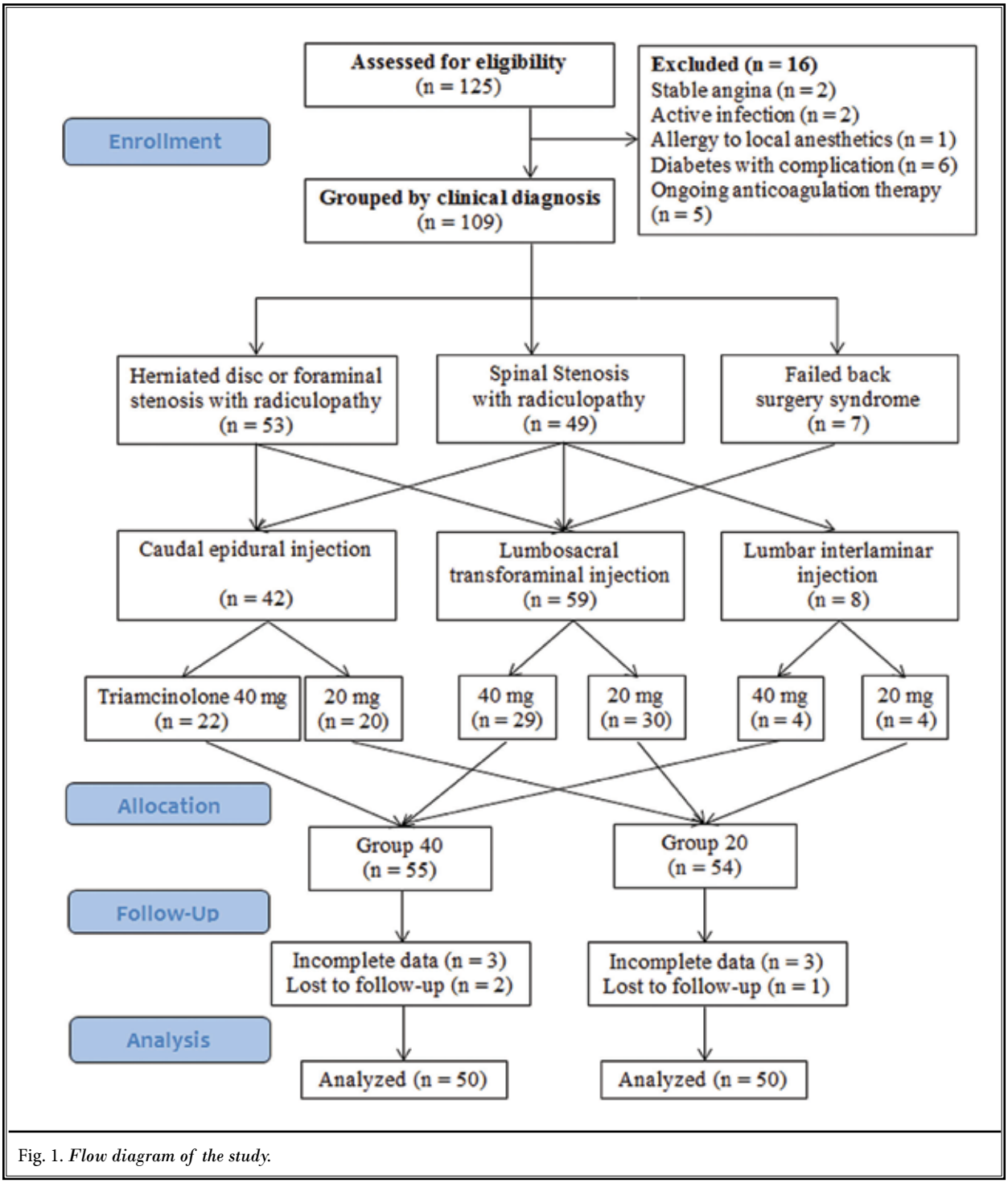

Fig. 1. *Flow diagram of the study.*

blood glucose levels at 2 separate times during the day, before breakfast and 2 hours after dinner. Recordings were made at the same time points for 3 days prior to the injection, as well as daily for one week and on day 14 following the injection (postprocedure day (PPD) #0 to #7 and #14). All glucose measurements were

recorded in milligrams per deciliter (mg/dL), which is the standard of care. We also requested that patients not alter their dietary or diabetic medication regimens from their normal routine. If the postprandial blood glucose level (PBG) or the fasting blood glucose level (FBG) after the injection exceeded 250 mg/dL for 4 days or longer, patients were asked to consult their managing physician for adjustment of oral hypoglycemics and/or insulin therapy. This was noted during our follow-up appointment. The blood glucose diaries were returned to the investigator at subsequent follow-up appointments.

Numeric rating scale (NRS) for subjective pain was measured on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable). The NRS score was recorded by all patients 2 hours after dinner along with the PBG measurements. Employment status and clinical outcome were determined at 8 weeks after enrollment at the outpatient clinic or by telephone interview.

Injection Protocol

The spinal level and approach for administration of epidural corticosteroid (lumbar interlaminar, lumbosacral transforaminal, or caudal epidural) were determined based on symptoms, spinal pathology, and magnetic resonance image findings. All procedures were performed under fluoroscopic guidance by one of 3 treating investigators. For each injection, the patient was placed in the prone position and subsequently prepped and draped in the standard sterile fashion. Using sterile technique and intermittent fluoroscopic guidance, a 3.5-inch epidural needle (17G for caudal epidural, 19G for lumbar interlaminar and 23G for lumbosacral transforaminal, Tuohy epidural needle, Tae-Chang Industrial Co., Seoul, Republic of Korea) was placed in the epidural space through a lumbar interlaminar, lumbosacral transforaminal, or caudal epidural approach. Nonioinic contrast medium was injected to confirm needle placement. This was followed by an injection of 40 mg or 20 mg of triamcinolone (40 mg/mL, Triam®, Dongkwang, Seoul, Republic of Korea).

All lumbar interlaminar and caudal ESIs consisted of a mixture of one mL of triamcinolone, 3.5 mL of 0.25% levobupivacaine, and 2.5 mL of normal saline for Group 40 or a mixture of 0.5 mL of triamcinolone, 3.5 mL of 0.25% levobupivacaine, and 3 mL of normal saline for Group 20. All transforaminal ESIs consisted of a mixture of one mL of triamcinolone and one mL of 0.25% levobupivacaine for Group 40 or a mixture of 0.5 mL triamcinolone, one mL of 0.25% levobupivacaine, and 0.5 mL normal saline for Group 20. After the procedure, the patients were given time for recovery and were then discharged. Patients recorded their blood glucose levels and NRS pain score 2 hours after dinner on the day of injection and at the subsequent time points described in the above protocol.

Statistical Analysis

This study was powered to detect a minimum difference in peak glucose level of 40 mg/dL between Group 40 and Group 20, with an alpha error of 5% and a beta error of 80%. The primary research hypothesis was that either fasting or postprandial changes in blood glucose peak level after the procedure would be different according to the steroid dose. Based on previous studies (14-16), PBG excursions on the day of procedure were assumed to differ by 40 ± 68 mg/dL between groups. To detect a treatment group difference of 40 mg/dL with a power of 80% at an alpha of 5%, 45 patients were needed per group. Assuming a drop-out rate of approximately 10%, 50 patients per group were determined.

Continuous data with normal distributions are presented as means (standard deviations), and nonparametric data are presented as median (interquartile ranges). Kolmogorov-Smirnov tests with Lilliefors correction and visual inspection of histograms and Q-Q plots were used to assess the normality of the data distribution. Patient characteristics were compared using unpaired t-test or Mann-Whitney U test for continuous variables according to the normality of the variable and $\chi 2$ test or Fisher's exact test for categorical variables according to their expected counts.

Comparisons of blood glucose levels were performed with repeated measures analysis of variance. For this comparison, Mauchly's test of sphericity revealed that the condition of sphericity had not been met. For comparisons between paired time points, we calculated the mean glucose level over the 3 days prior to ESI and treated it as the baseline glucose level for each individual. We then compared the glucose levels after ESI with the baseline values. Missing data for blood glucose levels were allowed for up to 3 values for each patient, and the next available data point was imputed. Comparisons of blood glucose levels between paired time points within each group were performed using paired t-tests. Comparisons of blood glucose levels between groups were performed using unpaired t-tests. Bonferroni corrections were used to reduce the false-positive results generated by multiple comparisons

of intergroup differences. A Spearman correlation was calculated to assess the associations among age, body mass index, preinjection hemoglobin A1c level and postprandial blood glucose level change from baseline on PPD #0. *P* values < 0.05 were considered to be statistically significant. For all statistical analyses, data were analyzed using SPSS software version 20.0, (SPSS Inc., Chicago, IL).

Results

Of the 125 patients assessed for eligibility, 16 were excluded due to stable angina pectoris (n = 2), active infection (n = 2), history of allergy to local anesthetics (n = 1), uncontrolled diabetes with complication (n = 6), or ongoing anticoagulation therapy (n = 5). Additionally, 9 patients were dropped from the study due to incomplete data or lost to follow-up. Thus, a total of 100 patients remained and were analyzed (Fig. 1). Patients' characteristics are shown in Table 1. The type of procedure performed was not different between groups. Hemoglobin A1c level was not different between groups, which allowed us to exclude any differences in blood glucose elevation due to well managed versus poorly managed diabetes.

The baseline postprandial interquartile glucose level before ESI (the average of values of 3 days before the injection) in all patients ranged from 147 to 214 mg/dL, with a mean of 181 mg/dL and a standard deviation of 53. The postprandial interquartile glucose level on the day of injection in all patients ranged between 215 to 326 mg/dL, with a mean of 265 mg/dL and a standard deviation of 81. The average change in glucose level was 84 ± 40 mg/dL, with a range of -35 to +147 mg/dL. Postprandial glucose level immediately after injection was increased by more than 30 mg/dL in 90 patients (90%) compared with the baseline value on the day of injection. It was higher than 180 mg/dL in 85 patients (85%) and higher than 250 mg/dL in 64 patients (64%).

Table 1. *Patient and clinical characteristics* .

	Group 40	Group 20	*P*-value
Sample size, n	50	50	
Female, n	31 (62)	32 (64)	0.836
Age, year	68 (60 – 78)	69 (63 – 75)	0.978
Body weight, kg	62 (54 – 70)	63 (54 – 68)	0.767
Height, cm	159 (9)	156 (9)	0.107
Body-mass index, kg/m2	24.5 (20.7 – 29.5)	25.9 (20.9 – 29.4)	0.400
Type II DM, n	48 (96)	46 (92)	0.678
Hemoglobin A1c, most recent value, %	7.15 (1.01)	7.39 (0.99)	0.238
DM medication			
Insulin / Oral hypoglycemic, n	2 / 48	4 / 46	0.678
Hypertension, n	15 (30)	16 (32)	0.829
Angina pectoris, n	8 (16)	7 (14)	0.999
Chronic kidney disease, n	1 (2)	2 (4)	0.999
Diagnosis			**0.667**
Herniated disc or foraminal stenosis with Radiculopathy, n	27 (54)	22 (44)	0.317
Spinal stenosis with radiculopathy, n	20 (40)	24 (48)	0.546
Failed back surgery syndrome, n	3 (6)	4 (8)	0.999
Procedure			**0.795**
Caudal epidural injection, n	20 (40)	18 (36)	0.680
Lumbosacral transforaminal injection, n	27 (54)	30 (60)	0.545
Lumbar interlaminar injection, n	3 (6)	2 (4)	0.999

Data are reported as mean (standard deviation), median (interquartile range), or number (%).
Group 40 = group with epidural triamcinolone 40 mg injection; Group 20 = group with epidural steroid 20 mg injection; DM = diabetes mellitus.
P-values are the results of unpaired t-test or Mann-Whitney U test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. The numbers of diagnosis and procedure in each group are different from those in Fig. 1 because this table contains only the analyzed cases except the excluded or dropped cases.

Table 2. *Daily blood glucose level change compared with baseline.*

Day	Group 40			Group 20			
Fasting glucose (mg/dl)	**Value**	**Change**	***P*-value[a]**	**Value**	**Change**	***P*-value[a]**	***P*-value[b]**
Baseline	129 (31)			131 (37)			0.776
PPD #1	179 (51)	+ 50 (38)	<0.001	146 (50)	+15 (20)	<0.001	0.001
PPD #2	154 (38)	+ 25 (28)	<0.001	135 (42)	+ 5 (16)	0.053	0.029
PPD #3	141 (43)	+ 12 (31)	0.011	130 (46)	- 1 (18)	0.669	0.218
PPD #4	134 (36)	+ 5 (28)	0.207	131 (31)	0 (21)	0.924	0.627
PPD #5	134 (36)	+ 5 (28)	0.217	129 (39)	- 2 (20)	0.629	0.571
PPD #6	135 (41)	+6 (29)	0.162	129 (36)	- 2 (21)	0.448	0.432
PPD #7	127 (41)	- 1 (29)	0.732	129 (28)	- 2 (16)	0.494	0.806
PPD #14	131 (31)	+ 2 (26)	0.554	127 (32)	- 4 (20)	0.181	0.520
Postprandial glucose (mg/dl)	**Value**	**Change**	***P*-value[a]**	**Value**	**Change**	***P*-value[a]**	***P*-value[b]**
Baseline	178 (43)			184 (63)			0.606
PPD #0	288 (57)	+ 110 (20)	<0.001	242 (94)	+ 59 (38)	<0.001	0.004
PPD #1	266 (70)	+ 88 (30)	<0.001	234 (71)	+ 50 (31)	<0.001	0.024
PPD #2	244 (51)	+ 66 (17)	<0.001	221 (84)	+ 37 (23)	<0.001	0.097
PPD #3	197 (62)	+ 19 (27)	<0.001	193 (76)	+ 9 (28)	0.023	0.789
PPD #4	186 (54)	+ 8 (26)	0.037	186 (76)	+ 2 (25)	0.543	0.994
PPD #5	184 (58)	+ 6 (29)	0.137	182 (62)	- 2 (17)	0.369	0.811
PPD #6	181 (64)	+ 3 (28)	0.425	179 (50)	- 5 (28)	0.229	0.839
PPD #7	179 (53)	0 (21)	0.786	182 (58)	- 2 (27)	0.709	0.768
PPD #14	182 (58)	+ 4 (26)	0.294	177 (51)	- 7 (30)	0.118	0.646

Data are reported as mean (standard deviation). Baseline values were calculated by the average blood glucose level of 3 days before procedure. *P*-values[a] are the results of paired t-tests compared with the value of one-day before the procedure within each group. *P*-values[b] are the results of unpaired t-test with the Bonferroni's correction of blood glucose level between the two groups. Group 40 = group with epidural triamcinolone 40 mg injection; Group 20 = group with epidural steroid 20 mg injection; PPD = post-procedure day .

Daily blood glucose levels for each group are reported in Table 2 and Figs. 2 and 3. There were statistically significant increases in both fasting and postprandial blood glucose levels after ESI in both groups. There were significant increases in FBG on PPD #1 to PPD #3 in Group 40, and on PPD #1 in Group 20 (Fig. 2). Moreover, the increase in FBG was significantly greater in Group 40 than Group 20 on PPD #1 and PPD #2 (FBG on PPD #1: 179 [51] mg/dL in Group 40 versus 146 [50] mg/dL in Group 20, $P < 0.001$). There were significant increases in PBG on PPD #0 to PPD #3 in both groups (Fig. 3). Notably, increases in PBG were significantly greater in Group 40 than Group 20 on PPD #0 and #1 (PBG on PPD #0: 288 [57] mg/dL versus 242 [94] mg/dL in Groups 40 and 20, respectively, $P = 0.004$).

The incidences of high blood glucose level are shown in Table 3. The incidence of fasting blood glucose > 180 mg/dL was significantly greater in Group 40 than in Group 20 on PPD #1 (Group 40, n = 25 vs. Group 20, n = 12, $P = 0.007$). Additionally, the incidence of postprandial blood glucose > 250 mg/dL was significantly greater in Group 40 than in Group 20 on PPD #1 (Group 40, n = 34 versus Group 20, n = 21, $P = 0.009$). In 13 patients (n= 6 in Group 40 and n = 7 in Group 20), PBG or FBG after the injection exceeded 250 mg/dL for 4 days or longer. Ten patients among them visited their managing physician and 4 of them had their medication adjusted.

Subjective pain scores were obtained according to NRS, which decreased significantly for 2 weeks after the injection. There were no significant differences in pain scores between groups (Fig. 4). There were no significant correlations among age, body mass index, and hemoglobin A1c and the changes in postprandial blood glucose level. Table 4 shows the employment status according to the injection type. In Group 40, 9 patients (18%) were employable at baseline with 3 patients employed and 6 unemployed due to pain. In Group 20, 8 patients (16%) were employable at baseline with 2 patients employed and 6 unemployed due to pain. There

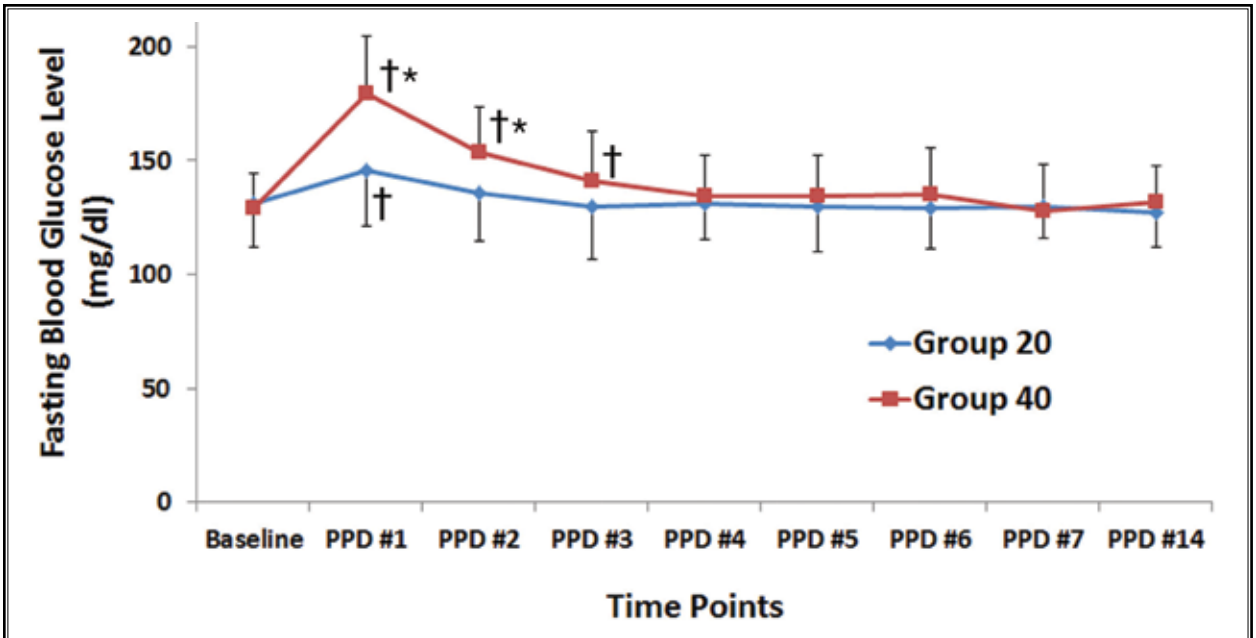

Fig. 2. *Daily morning fasting blood glucose (FBG) levels according to the study group. Values are presented as mean with standard deviation.*

Baseline = the day before the procedure; PPD = postprocedure day; PPD #0 = the day of the procedure; PPD #1 = one day after the procedure; Group 20 = group receiving 20 mg epidural triamcinolone; Group 40 = group receiving 40 mg epidural triamcinolone. *significantly different between groups. †significantly different from baseline value.

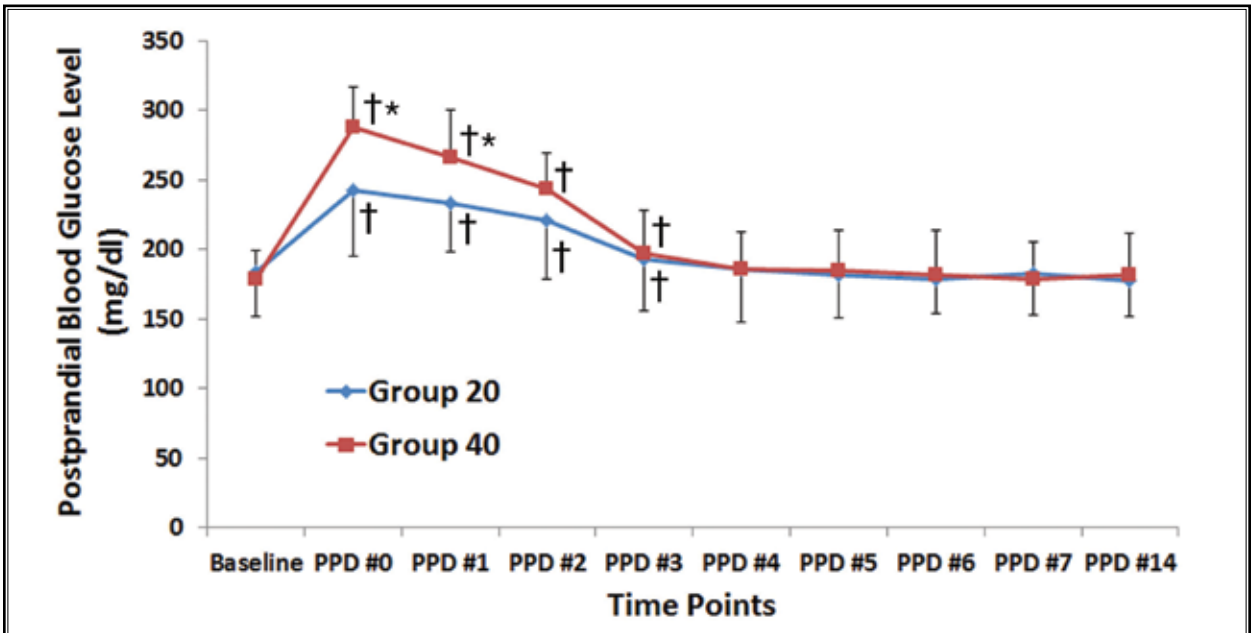

Fig. 3. Daily postprandial blood glucose levels (PBG, measured 2 hours after dinner) according to the study group. Values are presented as mean with standard deviation.

Baseline = the day before the procedure; PPD = postprocedure day; PPD #0 = the day of the procedure; PPD #1 = one day after the procedure; Group 20 = group receiving 20 mg epidural triamcinolone; Group 40 = group receiving 40 mg epidural triamcinolone. *significantly different between groups. †significantly different from the baseline value.

Table 3. *Incidence of high blood glucose level.*

Day	Group 40	Group 20	*P*-value	Group 40	Group 20	*P*-value
	Fasting glucose > 180 (mg/dl)			Fasting glucose > 200 (mg/dl)		
Baseline	5 (10)	5 (10)	0.999	0 (0)	2 (4)	0.495
PPD #1	25 (50)	12 (24)	0.007	20 (40)	6 (12)	0.001
PPD #2	14 (28)	9 (18)	0.235	6 (12)	3 (6)	0.487
PPD #3	11 (22)	7 (14)	0.436	4 (8)	3 (6)	0.999
PPD #4	5 (10)	3 (6)	0.715	2 (4)	1 (2)	0.999
PPD #5	6 (12)	6 (12)	0.999	1 (2)	2 (4)	0.999
PPD #6	7 (14)	5 (10)	0.538	3 (6)	1 (2)	0.617
PPD #7	6 (12)	4 (8)	0.741	1 (2)	0 (0)	0.999
PPD #14	2 (4)	2 (4)	0.999	1 (2)	0 (0)	0.999
>180 for 4 days or longer	5 (10)	3 (6)	0.715			
>180 for 5 days or longer	4 (8)	3 (6)	0.999			
	Postprandial glucose > 180 (mg/dl)			Postprandial glucose > 250 (mg/dl)		
Baseline	27 (54)	23 (46)	0.424	3 (6)	8 (16)	0.110
PPD #0	49 (98)	36 (72)	<0.001	36 (72)	28 (56)	0.096
PPD #1	46 (92)	37 (74)	0.031	34 (68)	21 (42)	0.009
PPD #2	45 (90)	33 (66)	0.004	24 (48)	18 (36)	0.224
PPD #3	34 (68)	32 (64)	0.673	11 (22)	14 (28)	0.488
PPD #4	25 (50)	23 (46)	0.689	7 (14)	7 (14)	0.999
PPD #5	28 (56)	24 (48)	0.423	8 (16)	7 (14)	0.779
PPD #6	28 (56)	22 (44)	0.230	5 (10)	5 (10)	0.999
PPD #7	25 (50)	27 (54)	0.689	3 (6)	7 (14)	0.318
PPD #14	27 (54)	23 (46)	0.424	6 (12)	2 (4)	0.269
>250 for 4 days or longer				6 (12)	7 (14)	0.766
>250 for 5 days or longer				4 (8)	4 (8)	0.999

Data are reported as number (%). *P*-values are the results of chi-square test or Fisher's exact test between groups according to their expected counts. Group 40 = group with epidural triamcinolone 40 mg injection; Group 20 = group with epidural steroid 20 mg injection; PPD = post-procedure day.

was a slight improvement in employment status in both groups with 3 patients in Group 40 and 2 patients in Group 20 becoming employed at 8 weeks after enrollment. Table 5 shows the clinical outcome of all patients in both groups. There was no significant difference in clinical outcome between groups.

Discussion

We evaluated the effects of 2 different doses of epidural steroid injections on blood glucose levels and pain control in patients with DM. Our results indicate that the blood glucose increase was greater in PBG than in FBG. A higher dose of triamcinolone produces a greater increase in blood glucose level than does a lower dose. The patient-reported pain score 2 weeks after the procedure did not differ between those receiving high or low doses of steroid. The clinical outcome and employment status did not differ between 2 groups. This suggests that higher doses of steroids have no advantage over lower doses of steroids in patients with DM, as it only further elevates the blood glucose level. The elevated postprandial blood glucose level was clinically relevant, as 85% of patients showed an elevation in blood glucose of more than 180 mg/dL. The upper limit for optimal fasting blood glucose control is known to be 180 mg/dL in noncritical diabetic patients (17).

A previous study reported that patients with spinal stenosis had a higher incidence of DM in all age groups (3). DM is known to cause pathology in many systems, including intervertebral discs and joints, resulting in early degeneration (18,19). Multiple degenerative disorders of the lumbar spine are initially managed nonsurgically. Epidural steroid injections via interlaminar, caudal, and transforaminal approaches are some of the

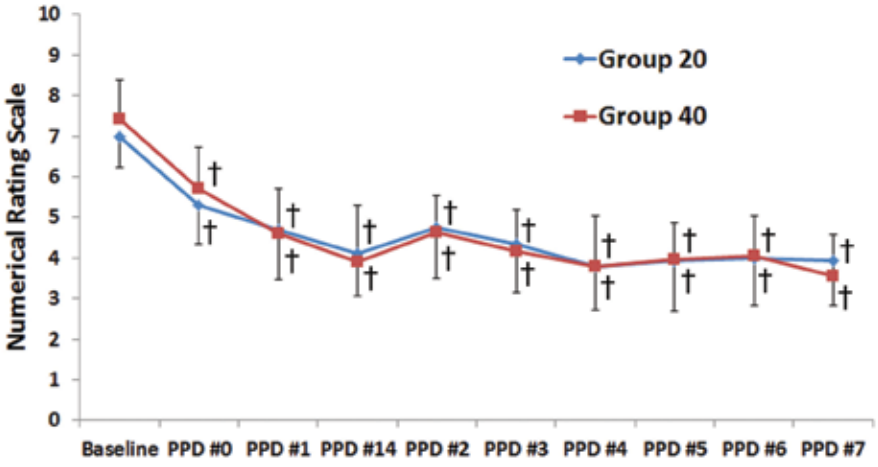

Fig. 4. *Daily numeric rating scale (0 – 10) of subjective pain reported by the patients according to the study group. Values are presented as mean with standard deviation.*

Baseline = the day before procedure; PPD = postprocedure day; PPD #0 = the day of the procedure; PPD #1 = one day after the procedure; Group 20 = group receiving 20 mg epidural triamcinolone; Group 40 = group receiving 40 mg epidural triamcinolone. †significantly different from the baseline value.

Table 4. *Employment status change at eight weeks after enrollment.*

	Caudal epidural injection (n = 38)				Lumbosacral transforaminal injection (n = 57)				Lumbar interlaminar injection (n = 5)			
	Group 40 (n = 20)		Group 20 (n = 18)		Group 40 (n = 27)		Group 20 (n = 30)		Group 40 (n = 3)		Group 20 (n = 2)	
	Baseline	8 wks	Baseline	8 wks	Baseline	8 wks	Baseline	8 wks	Baseline	8 wks	Baseline	8 wks
Employable												
Employed	1 (5)	2 (10)	0	1 (6)	2 (7)	4 (14)	2 (7)	3 (10)	0	0	0	0
Unemployed due to pain	3 (15)	2 (10)	3 (17)	2 (11)	3 (11)	1 (4)	3 (10)	2 (7)	0	0	0	0
Unemployable												
Housewife	2 (10)	2 (10)	3 (17)	3 (17)	6 (22)	6 (22)	6 (20)	6 (20)	0	0	1 (50)	1 (50)
Disabled	1 (5)	1 (5)	0	0	1 (4)	1 (4)	1 (3)	1 (3)	0	0	0	0
Over 65 years	13 (65)	13 (65)	12 (66)	12 (66)	15 (56)	15 (56)	18 (60)	18 (60)	3 (100)	3 (100)	1 (50)	1 (50)

Data are reported as number (%).
Group 40 = group with epidural triamcinolone 40 mg injection; Group 20 = group with epidural steroid 20 mg injection.
Seven patients were lost to follow-up at 8 weeks after enrollment, but they were included as housewife or those over 65 years.

Table 5. Clinical outcome at eight weeks after enrollment.

	Caudal epidural injection (n = 38)		Lumbosacral transforaminal injection (n = 57)		Lumbar interlaminar injection (n = 5)	
	Group 40 (n = 20)	Group 20 (n = 18)	Group 40 (n = 27)	Group 20 (n = 30)	Group 40 (n = 3)	Group 20 (n = 2)
Discharged	2 (10)	1 (6)	2 (7)	2 (7)	0	0
Follow up with Medication only	11 (55)	11 (60)	13 (48)	15 (50)	2 (67)	2
Further epidural steroid injection	5 (25)	4 (22)	7 (26)	8 (26)	1 (33)	0
Surgery (discectomy or decompression)	1 (5)	1 (6)	3 (11)	2 (7)	0	0
Lost to follow-up	1 (5)	1 (6)	2 (7)	3 (10)	0	0

Data are reported as number (%).
Group 40 = group with epidural triamcinolone 40 mg injection; Group 20 = group with epidural steroid 20 mg injection.

many initial treatment options. Despite the proven efficacy of ESIs for the treatment of lumbar degenerative disorders (20,21), the complications that accompany this treatment modality must be considered (22).

In patients with DM, an increase in plasma glucose levels following ESI should be considered as a potential complication. The use of oral or intravenous steroids diminishes peripheral glucose metabolism and stimulates gluconeogenesis, ultimately elevating blood glucose levels and can cause steroid-induced DM (23). In addition, glucocorticoids increase the blood glucose level by acting as insulin antagonists, inhibiting peripheral glucose uptake (24). This blood glucose elevation is compensated for by increasing endogenous insulin production, which is found in most patients but not in patients with DM. New-onset DM could occur in patients without DM after corticosteroid therapy (25,26).

Previous studies have shown variable changes in plasma glucose levels in diabetic patients undergoing intraarticular injections of corticosteroids (2,24,27). Wang et al (24) evaluated the effect of trigger finger injections with methylprednisolone on the rise in blood glucose and found that all patients demonstrated an elevation in blood glucose level, with an increase of 73% more than the preinjection levels (24). Meanwhile, Habib et al (27) reported injection of methylprednisolone at the shoulder joint in patients with diabetes has no significant effect on blood glucose level. This difference may be due to a small sample size and different degree of diabetic control.

In contrast, studies that have evaluated the effects of epidural steroids have shown elevations in blood glucose level consistently. Gonzales et al (11) demonstrated that blood glucose elevations remained statistically significant for 3 days after transforaminal or caudal epidural injections in 12 patients with diabetes. Additionally, Even et al (12) demonstrated that patients had a mean 79% increase in blood glucose level following an interlaminar epidural steroid injection. However, these studies did not separately evaluate fasting and postprandial blood glucose. Our study confirmed the elevation in blood glucose level (10-12) and that the increase is greater in PBG than in FBG (10).

While this increase lasted only up to 4 days in most patients, even short-term elevations in blood glucose may be associated with adverse sequelae (28-30). Furthermore, as ESIs could be performed repetitively in patients with radiculopathy, spinal stenosis, or failed back surgery syndrome, repetitive episodes of hyperglycemia occur in these patients. Fluctuations in plasma glucose levels have been reported to be associated with increased cardiovascular mortality (30). Increases in plasma glucose levels have been shown to be a risk factor for perioperative infection in patients undergoing spine surgery (31). Theoretically, this could increase the risk of infection for any invasive procedure. Corticosteroids also affect the hypothalamic-pituitary-adrenal axis (10), which can lead to transient elevations in glucose and difficulties with glycemic control, especially in patients with diabetes (32,33). It may put the patient at risk for up to 4 weeks for adrenal insufficiency if exposed to stressful events (34,35).

Considering multiple ESIs can result in repetitive hyperglycemia (36), the effort to minimize these blood glucose excursions would be beneficial. Although treatment of hyperglycemia caused by short-term medication (< one month) is debatable (28), currently available agents used in the treatment of type 2 DM have been suggested as a treatment for glucocorticoid-induced hyperglycemia (37). Also, use of insulin to prevent it is another treatment option available. Further studies are required to establish a strategy for treatment of ESIs-induced hyperglycemia.

As there is no established treatment of ESIs-induced hyperglycemia, it would be currently best to prevent or minimize the elevation of blood glucose level after ESIs. Our results support that lower doses of corticosteroids can reduce the blood glucose excursions after ESIs for those with DM. Similary, Kang et al (13) compared the effects of using different triamcinolone dosages in transforaminal epidural steroid injections and concluded that there were no differences among 10, 20, and 40 mg dosages. Our study also showed that subjective pain and clinical outcome after ESI were not different between patients receiving 20 or 40 mg doses of triamcinolone. Therefore, an ESI injection using 20 mg of triamcinolone is preferable to 40 mg, especially in patients with diabetes.

The present study has several limitations. First, the patients who chose to participate in this study may be a cohort who have well-controlled diabetes, as they were willing to measure their blood sugar levels twice daily for 2 weeks. This may have resulted in a selection bias, leading to increases in blood glucose levels that were less than those of patients with poorly controlled diabetes. Good diabetes control was defined as hemoglobin A1c of less than 7% (38); there were 42 patients who met this criteria in our study population. Therefore, our study population evenly included patients with both well and poorly controlled diabetes. Second, we did not

compare use of the 2 steroid dosages in a single kind of procedure. The different routes of administration within the epidural space could result in different levels of systemic absorption, thereby influencing the level and duration of hyperglycemia. Furthermore, systemic absorption of steroid can vary in patients with failed back surgery syndrome compared with non-failed back surgery syndrome groups. However, there was no statistical difference in the kinds of procedure performed or number of failed back surgery syndrome patients between groups. Furthermore, we found no studies reporting blood glucose differing according to the location of epidural injection.

Conclusion

In conclusion, epidural steroid injections were associated with statistically significant and clinically relevant elevations in blood glucose level in patients with diabetes for up to 4 days after the procedure. As the elevation of PBG was more prominent than that of FBG, monitoring of PBG is more important than that of FBG in patients with ESI. Although the increases in FBG and PBG were significantly greater with 40 mg compared with 20 mg of triamcinolone, pain control, clinical outcome, and employment status change after ESI were not different between the 2 dosages. Based on our results, 20 mg of triamcinolone should be used rather than 40 mg in patients with diabetes.

References

1. Ciol MA, Deyo RA, Howell E, Kreif S. An assessment of surgery for spinal stenosis: Time trends, geographic variations, complications, and reoperations. *J Am Geriatr Soc* 1996; 44:285-290.
2. Black DM, Filak AT. Hyperglycemia with non-insulin-dependent diabetes following intraarticular steroid injection. *J Fam Pract* 1989; 28:462-463.
3. Lotan R, Oron A, Anekstein Y, Shalmon E, Mirovsky Y. Lumbar stenosis and systemic diseases: Is there any relevance? *J Spinal Disord Tech* 2008; 21:247-251.
4. Igarashi T, Hirabayashi Y, Seo N, Saitoh K, Fukuda H, Suzuki H. Lysis of adhesions and epidural injection of steroid/local anaesthetic during epiduroscopy potentially alleviate low back and leg pain in elderly patients with lumbar spinal stenosis. *Br J Anaesth* 2004; 93:181-187.
5. Botwin KP, Gruber RD, Bouchlas CG, Torres-Ramos FM, Sanelli JT, Freeman ED, Slaten WK, Rao S. Fluoroscopically guided lumbar transformational epidural steroid injections in degenerative lumbar stenosis: An outcome study. *Am J Phys Med Rehabil* 2002; 81:898-905.
6. Manchikanti L, Cash KA, McManus CD, Pampati V, Fellows B. Results of 2-year follow-up of a randomized, double-blind, controlled trial of fluoroscopic caudal epidural injections in central spinal stenosis. *Pain Physician* 2012; 15:371-384.
7. Benyamin RM, Manchikanti L, Parr AT, Diwan S, Singh V, Falco FJ, Datta S, Abdi S, Hirsch JA. The effectiveness of lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain. *Pain Physician* 2012; 15:E363-404.
8. Manchikanti L, Buenaventura RM, Manchikanti KN, Ruan X, Gupta S, Smith HS, Christo PJ, Ward SP. Effectiveness of therapeutic lumbar transforaminal epidural steroid injections in managing lumbar spinal pain. *Pain Physician* 2012; 15:E199-245.
9. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. Effect of fluoroscopically guided caudal epidural steroid or local anesthetic injections in the treatment of lumbar disc herniation and radiculitis: a randomized, controlled, double blind trial with a two-year follow-up. *Pain Physician* 2012; 15:273-286.
10. Younes M, Neffati F, Touzi M, Hassen-Zrour S, Fendri Y, Bejia I, Ben Amor A, Bergaoui N, Najjar MF. Systemic effects of epidural and intra-articular glucocorticoid injections in diabetic and non-diabetic patients. *Joint Bone Spine* 2007; 74:472-476.
11. Gonzalez P, Laker SR, Sullivan W, Harwood JE, Akuthota V. The effects of epidural betamethasone on blood glucose in patients with diabetes mellitus. *PM R* 2009; 1:340-345.
12. Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. *Spine (Phila Pa 1976)* 2012; 37:E46-50.
13. Kang SS, Hwang BM, Son HJ, Cheong IY, Lee SJ, Lee SH, Chung TY. The dosages of corticosteroid in transforaminal epidural steroid injections for lumbar radicular pain due to a herniated disc. *Pain Physician* 2011; 14:361-370.
14. Lukins MB, Manninen PH. Hyperglycemia in patients administered dexamethasone for craniotomy. *Anesth Analg* 2005; 100:1129-1133.
15. Kazda C, Hulstrunk H, Helsberg K, Langer F, Forst T, Hanefeld M. Prandial insulin substitution with insulin lispro or insulin lispro mid mixture vs. basal therapy with insulin glargine: A randomized controlled trial in patients with type 2 diabetes beginning insulin therapy. *J Diabetes Complications* 2006; 20:145-152.
16. Nazar CE, Lacassie HJ, Lopez RA, Munoz HR. Dexamethasone for postoperative nausea and vomiting prophylaxis: Effect on glycaemia in obese patients with impaired glucose tolerance. *Eur J Anaesthesiol* 2009; 26:318-321.
17. Garber AJ, Moghissi ES, Bransome ED, Jr., Clark NG, Clement S, Cobin RH, Furnary AP, Hirsch IB, Levy P, Roberts R, Van den Berghe G, Zamudio V. American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract* 2004; 10:77-82.
18. Robinson D, Mirovsky Y, Halperin N, Evron Z, Nevo Z. Changes in proteoglycans of intervertebral disc in diabetic patients. A possible cause of increased

back pain. *Spine (Phila Pa 1976)* 1998; 23:849-855; discussion 856.

19. Jeffcoate WJ, Game F, Cavanagh PR. The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charcot foot) in diabetes. *Lancet* 2005; 366:2058-2061.
20. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: A prospective randomized study. *Spine (Phila Pa 1976)* 2002; 27:11-16.
21. Riew KD, Park JB, Cho YS, Gilula L, Patel A, Lenke LG, Bridwell KH. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am* 2006; 88:1722-1725.
22. Abdi S, Datta S, Lucas LF. Role of epidural steroids in the management of chronic spinal pain: A systematic review of effectiveness and complications. *Pain Physician* 2005; 8:127-143.
23. Iwamoto T, Kagawa Y, Naito Y, Kuzuhara S, Kojima M. Steroid-induced diabetes mellitus and related risk factors in patients with neurologic diseases. *Pharmacotherapy* 2004; 24:508-514.
24. Wang AA, Hutchinson DT. The effect of corticosteroid injection for trigger finger on blood glucose level in diabetic patients. *J Hand Surg Am* 2006; 31:979-981.
25. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. *Diabetes Care* 2006; 29:2728-2729.
26. Blackburn D, Hux J, Mamdani M. Quantification of the risk of corticosteroid-induced diabetes mellitus among the elderly. *J Gen Intern Med* 2002; 17:717-720.
27. Habib GS, Abu-Ahmad R. Lack of effect of corticosteroid injection at the shoulder joint on blood glucose levels in diabetic patients. *Clin Rheumatol* 2007; 26:566-568.
28. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. *Endocr Pract* 2009; 15:469-474.
29. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, Boemi M, Giugliano D. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 2008; 57:1349-1354.
30. Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R. Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus: The Verona Diabetes Study. *Circulation* 1997; 96:1750-1754.
31. Olsen MA, Nepple JJ, Riew KD, Lenke LG, Bridwell KH, Mayfield J, Fraser VJ. Risk factors for surgical site infection following orthopaedic spinal operations. *J Bone Joint Surg Am* 2008; 90:62-69.
32. Gottlieb NL, Riskin WG. Complications of local corticosteroid injections. *JAMA* 1980; 243:1547-1548.
33. Spaccarelli KC. Lumbar and caudal epidural corticosteroid injections. *Mayo Clin Proc* 1996; 71:169-178.
34. Chernow B, Vigersky R, O'Brian JT, Georges LP. Secondary adrenal insufficiency after intrathecal steroid administration. *J Neurosurg* 1982; 56:567-570.
35. Wicki J, Droz M, Cirafici L, Vallotton MB. Acute adrenal crisis in a patient treated with intraarticular steroid therapy. *J Rheumatol* 2000; 27:510-511.
36. Novak S, Nemeth WC. The basis for recommending repeating epidural steroid injections for radicular low back pain: A literature review. *Arch Phys Med Rehabil* 2008; 89:543-552.
37. Hoogwerf B, Danese RD. Drug selection and the management of corticosteroid-related diabetes mellitus. *Rheum Dis Clin North Am* 1999; 25:489-505.
38. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; 26 Suppl 1:S5-20.