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Effect of posterior subtenon injection of 40 mg of triamcinolone acetonide on glycemic control and serum cortisol and adrenocorticotropic hormone in diabetic patients

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Abstract. – OBJECTIVE: To evaluate the influence of posterior subtenon injection of 40 mg of triamcinolone acetonide (TA) on blood glucose, cortisol and adrenocorticotrophic hormone (ACTH) in patients with clinically significant diabetic macular oedema.

PATIENTS AND METHODS: This prospective clinical study included 33 type 2 diabetic patients assigned to receive subtenon injection of 40 mg of TA (study group: 20 patients, 9 women and 11 men, mean age 60.8 ± 10.1 years) or subtenon injection of 1 ml of saline solution (control group: 13 patients, 7 women and 6 men, mean age 57.9 ± 7.5 years) as an adjunct to focal/grid laser therapy. Pre-injection laboratory tests consisted of fasting blood glucose (FBG), glicolised hemoglobin (HbA1c), fructosamine, ACTH and cortisol. Post-injection measurements were performed in a following schedule: FBG in day 1; FBG, ACTH and cortisol at week 1; FBG, fructosamine, ACTH and cortisol at month 1, 2 and 3. HbA1c was also measured at 3 months. The mean ± SD values of groups at each visit were compared. The time-related changes in the parameters in each group were also analyzed using SPSS (Statistical Package for Social Sciences) for Windows 15.0 software.

RESULTS: Pre-injection FBG, HbA1c, fructosamine, ACTH and cortisol were similar in both groups ($p > 0.05$ for all). Pre-injection and final HbA1c values were similar in the study (8.6% ± 1.9 and 8.7% ± 1.8, respectively) and control groups (8.6% ± 1.7 and 8.5% ± 1.8, respectively) ($p > 0.05$ for all). None of the patients had a decrease in plasma cortisol that decreased below normal values at either time point. There was no statistically significant difference between groups and between each visit in groups according to FBG levels, blood fructosamine, ACTH and cortisol levels ($p > 0.05$ for all). No adverse event was observed.

CONCLUSIONS: Subtenon injection of 40 mg of TA does not increase blood sugar levels significantly, and it does not suppress blood cortisol or ACTH levels at 1 week or later in patients with diabetes mellitus. Subtenon injection of 40 mg TA seems to be safe in respect to elevation of blood sugar levels or systemic corticosteroid pathways.

Key Words:
Posterior subtenon injection, Triamcinolone acetonide, Type 2 diabetes, Systemic complications.

Introduction

Corticosteroids have been used in ophthalmology for several indications due to their strong anti-inflammatory effects. An important indication for intravitreal or peribulbar corticosteroid injection is diabetic macular oedema (DME), which is the main reason for decreasing visual acuity in patients with diabetic retinopathy[1]. The Early Treatment of Diabetic Retinopathy Study (ETDRS) group showed that focal photocoagulation is a beneficial treatment method for clinically significant macular oedema[2]. However, many patients still need corticosteroids or anti-vascular endothelial factor drugs as adjunctive therapy to laser photocoagulation or even monotherapy[1]. Triamcinolone acetonide (TA) is a long-acting synthetic glucocorticoid depot and 5 times potent than cortisol[3]. The main routes used for delivery of TA to the eye are intravitreal and subtenon injections[1].

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Although there are many studies related to the ocular side effects of intravitreal TA, the systemic effect of periocular injection of TA are not well known. Subtenon injection of high doses (20-40 mg) of TA for DME or ocular inflammatory disease is a common practice in many ophthalmology clinics[1,4]. Some studies reported hyperglycemia or suppression of hypothalamo-pituitary-adrenal (HPA) axis after local injection of TA[5-8]. In this study we aimed to investigate the effects of subtenon injection of 40 mg of TA on fasting blood glucose, blood cortisol, adrenocorticotropic hormone (ACTH), fructosamine and HbA1c levels in 3 months period.

Patients and Methods

Patient Population

The study adhered to the Declaration of Helsinki. Institutional Review Board approved the study. All patients were informed about the study protocol and a signed informed consent was obtained from each patient before their participation in the study.

All the study and control subjects were type 2 diabetic patients assigned to focal/grid laser photocoagulation for DME. The study group (20 patients, 9 women and 11 men, mean age 60.8 ± 10.1 years) received subtenon injection of 40 mg (1 ml) of TA (Kenacort-A, Bristol Myers Squibb, Princeton, NJ, USA) as an adjunct to laser therapy. The control group (13 patients, 7 women and 6 men, mean age 57.9 ± 7.5 years) received subtenon injection of 1 ml of saline solution. All injections were performed by the same ophthalmologist (BK) with subconjunctival anesthesia of 1 ml of lidocaine 4% in a special room designed for ocular injections. The laser photocoagulation was performed 2 weeks after the injections.

Exclusion criteria included patients with glaucoma, a history of ocular or systemic steroid treatment during the last 6 months, a history of change of anti-diabetic medication during the last 3 months and patients with abnormalities in any of the following laboratory tests performed: glycated hemoglobin (HbA1c) greater than 11%, fasting blood glucose (FBG) greater than 250 mg/dL, plasma ACTH greater than 46 pg/mL and plasma cortisol higher than 19 µg/dL. Patients with renal failure and any abnormality in computerized blood count were also excluded.

All the blood samples were taken at morning between 08:00-09:00 o'clock. In order to avoid stress-related change in the laboratory tests performed, the pre-injection blood samples were obtained 1 week before the injections. Pre-injection tests consisted of FBG, HbA1c, fructosamine, ACTH and cortisol. Post-injection measurements were performed in a following schedule: FBG in day 1; FBG, ACTH and cortisol at week 1; FBG, fructosamine, ACTH and cortisol at month 1, 2 and 3. Glycated hemoglobin was also measured at months 3. The mean values of groups at each visit were compared. The time-related changes in the parameters in each group were also analyzed.

All the study and control patients were asked or checked for unexpected weight gain, hirsutism, pedal oedema, easy brusing, irregular menses, mood changes or cushingoid appearance.

Statistical Analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistical methods (mean, standard deviation, frequency) were used to evaluate the data and chi-square test was used to compare the quantitative parameters. Mann-Whitney U test, Wilcoxon Signed Ranks test, Friedman test were used for non-parametric qualitative parameters. p values < 0.05 were considered as statistically significant.

Results

The demographic and clinical characteristics of the study and control subjects are summarized in Table I. Age, sex, duration of diabetes mellitus (DM) and type of anti-diabetic treatment were similar in both groups ($p > 0.05$ for all). No patients changed type of anti-diabetic treatment during the study. Results of the laboratory parameters measured are summarized in Table II. Pre-injection FBG, HbA1c, fructosamine, ACTH and cortisol were similar in both groups ($p > 0.05$ for all). Sexteen patients (80%) in the study and 10 patients (77%) in the control group had complete FBG, HbA1c, fructosamine, ACTH and cortisol measurements. Pre-injection and final HbA1c values were similar in the study (8.6% ± 1.9 and 8.7% ± 1.8, respectively) and control groups (8.6% ± 1.7 and 8.5% ± 1.8, respectively) ($p > 0.05$ for all). The FBG exceeded 250 mg/dL in 5 patients (25%) in the study and 3 patients (23%) in the control group during the follow-up.

Table I. The demographic and clinical characteristics of the study and control subjectst.

	Study group (n = 20) [number or mean ± SD]	Control group (n = 13) [number or mean ± SD]	*p* value
Age (year)	60.8 ± 10.1	57.9 ± 7.5	0.347**
Sex (female/male)	9/11	7/6	0.619*
Duration of DM (year)	12.9 ± 5.1	14.4 ± 4.6	0.394**
Antidiabetic medication (OAD/insulin)	9/11	6/7	0.948*

DM: diabetes mellitus; OAD oral antidiabetic drug; *Chi-Square test; **Mann-Whitney U test.

Plasma ACTH levels exceeded 46 pg/mL only in 2 patients (15%) in the control group. Plasma cortisol levels exceeded 19 µg/dL in 3 patients (15%) in the study and 2 patients (15%) in the control group. None of the patients had a decrease in plasma cortisol that decreased below normal values at either control point. There was no statistically significant difference between

Table II. The laboratory results of both groups.

	Study group (n = 20)		Control group (n = 13)		
	Mean ± SD	*p* value**	Mean ± SD	*p* value**	*p* value*
HbA1c					
Pre-injection	8.6 ± 1.9		8.6 ± 1.7		0.810
3rd month	8.7 ± 1.8		8.5 ± 1.8		0.868
p value**	0.743		0.806		
Fructosamin					
Pre-injection	251 ± 50		258 ± 80		0.827
1st month	253 ± 47	0.925	276 ± 77	0.203	0.476
2nd month	243 ± 55	0.363	257 ± 72	0.859	0.794
3rd month	261 ± 44	0.328	263 ± 78	0.625	0.885
p value***	0.504		0.085		
FBG					
Pre-injection	175 ± 60		174 ± 66		0.971
1st day	170 ± 47	0.149	169 ± 56	0.333	0.920
1st week	169 ± 37	1.0	167 ± 59	0.695	0.593
1st month	164 ± 52	0.220	171 ± 66	0.844	0.868
2nd month	170 ± 71	0.831	176 ± 70	0.724	0.688
3rd month	169 ± 81	0.421	186 ± 74	0.610	0.425
p value***	0.803		0.576		
Cortisol					
Pre-injection	15.1 ± 3		15.3 ± 2.7		0.983
1st week	14.8 ± 2.4	0.779	15.1 ± 4.6	0.889	0.674
1st month	14.5 ± 4.6	0.917	15.7 ± 5.6	0.894	0.685
2nd month	16.9 ± 2.2	0.594	14.7 ± 4.6	0.969	0.129
3rd month	17.4 ± 4.2	0.170	16± 5.2	0.701	0.412
p value***	0.878		0.376		
ACTH					
Pre-injection	22.9 ± 9		21.3 ± 11.4		0.735
1st week	24.5 ± 7.1	1.0	21.2 ± 4.9	0.499	0.452
1st month	20.2± 8.2	0.311	26.4 ± 23.7	0.328	0.865
2nd month	24.6 ± 7.1	0.271	23.9 ± 16	0.678	0.526
3rd month	21.4 ± 6.6	0.776	21.4 ± 10.3	0.530	0.661
p value***	0.160				0.959

HbA1c: glicolised hemoglobin; FBG: fasting blood glucose; ACTH: adrenocorticotphic hormone; *Mann-Whitney U test, **Wilcoxon Signed Ranks Test, ***Friedman test.

groups and between each visit in groups according to FBG levels, blood fructosamine, ACTH and cortisol levels ($p > 0.05$ for all). No adverse event was reported by the patients. Also no cushingoid appearance or sign was observed in any of the patients.

Discussion

Zaka-ur-Rab et al[9] administered 40 mg of TA to the posterior subtenon space of 35 non-diabetic eyes after conventional cataract surgery and measured serum TA levels at 1, 2, 3, 24, and 48 hours and 1, 2, and 6 weeks after injection. Significant levels of TA were detected in 45.71% of samples at 1 hour after injection, in 85.71% of samples at 2 hour after injection, in 100% of samples at 3 and 24 hours after injection, in 62.86% of samples at 48 hours after injection, and in 28.57% at 1 week after injection. Nan et al[10] measured the concentration of TA in the various ocular tissues and blood in twenty-one Chinchilla adult pigmented rabbits undergone subtenon injection of 40 mg TA. Triamcinolone was detectable in the fellow eyes and was also detectable at very low levels in all blood samples during the 30 days follow-up. These results suggest that TA could be present in patient circulation after subtenon injection, and this could affect systemic HPA axis function, which can lead to transient elevations in glucose and difficulties with glycemic control in diabetic patients[10-13]. Systemic use of glucocorticoids is known to worsen glycemic control in diabetic patients[3,14]. Additionally, some studies[7,8,15] reported hyperglycemia after periocular use of different type of glucocorticoids. Therefore, as a common opinion, periocular injection of steroids is not accepted as a purely local treatment[5].

Previous studies[11,16-19] that have investigated glycemic control after intra-articular injections of corticosteroids have shown variable changes in plasma glucose levels in diabetic patients. In contrast, studies[20-22] that have evaluated the effect of epidural steroids have reported elevations in blood glucose consistently. These contradictory results suggest that systemic effects of locally injected steroids may vary according to injection site. Feldman-Billard et al[8,14] showed that periocular injection of 4 mg of dexamethasone have hyperglycemic effects similar to those of intravenous pulse methylprednisolone in diabetic patients. Toda et al[4] reported no significant increase of FBG or HbA1c in diabetic patients who undergone subtenon injection of 12 to 20 mg of TA. Asensio-Sanchez et al[23] showed that capillary blood glucose increases at the day 1 post-treatment and remains elevated for 4 day in both diabetic and non-diabetic patients after retrobulbar injection of 40 mg of TA. In contrast, we did not observe significant change in FBG, fructosamine and HbA1c in our study group receiving subtenon injection of 40 mg TA. Baseline characteristics of our patients are different from those of other similar studies. While baseline FBG and HbA1c were 174 mg/dl, 175 mg/dL and 8.6%, 8.6%, respectively, in our study and control patients, these numbers ranged between 129 mg/dl and 138 mg/dL and 6.2% and 7.15% in other studies[4,11,23]. The baseline characteristics of our groups actually represent the poor metabolic control of diabetes in our patients. One might hypothesize that the hyperglycemic effect of periocular injection of 40 mg of TA is more difficult to recognize in patients with already poor metabolic control, as seen in our patients.

The HPA axis suppression potency of TA is fourfold greater than that of cortisol[24,25]. Suppression of HPA is a well-known complication of systemic glucocorticoid therapy[25]. Moreover, single or repeated local injection or repeated inhaled triamcinolone has also been shown to cause HPA suppression and iatrogenic Cushing syndrome[26-30]. Reddy et al[6] applied 30 to 60 mg of TA (85% of patients received 60 mg) to the deltoid muscle of 14 patients with dermatologic diseases, 6 of who received a second injection at 6 weeks. Morning plasma cortisol and ACTH were measured before injection and at 6 and 12 week after the injections. They determined significant decrease in morning cortisol levels at 6 and 12 post-injection weeks. No change in ACTH levels or iatrogenic Cushing syndrome or secondary adrenal insufficiency was observed. Interestingly, mean cortisol and ACTH levels were not significantly different at 12 weeks compared with 6 weeks, suggesting no further HPA axis suppression with repeated injection. Moreover, there was no meaningful correlation between either cortisol or ACTH and either body mass index or dose administered. Amiran et al[5] evaluated HPA axis function by means of the ACTH stimulation test following a single intravitreal injection of 4 mg of TA in 28 patients, 22 (78.6%) of whom were diabetic. One day following injection, the peak response to ACTH at 30 min was blunted in four patients (14.3% of

the study group, $p = 0.05$) and the cortisol response at 60 min was suppressed ($p = 0.009$). The authors concluded that a single intravitreal injection of 4 mg of TA may be associated with impaired HPA axis function in some patients during the first 24 h following injection[5]. No change in serum cortisol and ACTH was observed at any time point in our study patients. The results of Amiran et al[5] are in discordance with the results of Reddy et al[6] and our study, in which even much higher doses of TA were given. This may be due to the differences in methods used to evaluate changes in HPA axis. While Amiram et al[5] used ACTH stimulation test, the method used by us was direct measuring of morning serum cortisol and ACTH. The ACTH stimulation test is accepted as the best criterion for evaluation of the HPA axis[31,32]. Moreover, it shows the vulnerability and subclinical suppression of the HPA axis, whereas direct changes in serum cortisol and ACTH levels represent apparent HPA axis dysfunction or clinical condition[5,25].

We did not evaluate serum cortisol and ACTH during the first 6 post-injection days, which perhaps could lead the early changes in cortisol and ACTH levels to be overlooked. Our findings show that subtenon injection of 40 mg of TA do not induce any systemic corticosteroid pathways nor clinically significant blood sugar levels other than 1 week or later. Even if there were some systemic effects due to subtenon injection of TA, these effects should be limited to first days or even hours.

Conclusions

The subtenon injection of 40 mg of TA does not significantly alter serum FBG, fructosamine, HbA1c, cortisol and ACTH in diabetic patients. However, subclinical suppression of HPA axis in diabetic patients' undergone injection of high doses of TA cannot be excluded by the results of this study, especially for the first 24 hours. Therefore, more comprehensive studies with larger sample size are certainly needed to determine whether the subtenon route of TA injection is related to clinically important metabolic effects to suggest more appropriate way for TA delivery.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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