·Clinical Research·

Short-term effects of intravitreal triamcinolone acetonide injection on ocular blood flow evaluated with color Doppler ultrasonography

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Abstract

• AIM: To evaluate the changes in ocular blood flow with color Doppler ultrasonography (CDU) after intravitreal triamcinolone acetonide (IVTA) injection.

• METHODS: A total of 46 patients who underwent IVTA (4 mg/0.1 mL) injection for diabetic macular edema (DME) (n=22), central retinal vein occlusion (CRVO) (n=12) and choroidal neovascular membrane (CNVM) (n=12) were included in the study. Peak systolic velocity (PSV), end diastolic velocity (EDV) and resistivity index (RI) were measured from the ophthalmic artery (OA), the central retinal artery (CRA) and the posterior ciliary artery (PCA) of each patient with CDU before, at the end of the first week and at the end of the first month following IVTA injection.

• RESULTS: In the DME group, PSV of OA at the first of the first month (mean±SD) (37.48±10.87 cm/s) increased compared to pre-injection value (31.39±10.84 cm/s) (P=0.048). There was a statistically significant decrease (P=0.049) in PSV of CRA at the end of the first month (7.97±2.67 cm/s) compared to the pre-injection (9.47±3.37 cm/s). There was not any statistically significant difference on the other parameters in the DME group. Also, there was not any statistically significant difference on the ocular blood flow values in the CRVO and CNVM groups.

• CONCLUSION: We observed that 4 mg/0.1 mL IVTA increased PSV of OA and decreased PSV of CRA in DME patients and did not have any effect on ocular blood flow values of CRVO and CNVM patients.

• KEYWORDS: intravitreal triamcinolone acetonide; ocular blood flow; diabetic macular edema; central retinal vein occlusion; choroidal neovascular membrane
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INTRODUCTION

Corticosteroids have been used for treatment of many ocular diseases. They are applied topically as drops, given systemically or injected into the subconjunctival or sub-Tenon space. However, the intraocular concentration of steroids was not high enough to achieve a therapeutic level, or the systemic side effects were too prominent for a prolonged treatment. To overcome this limitation authors suggested the intravitreal application of steroids[1-3].

Because soluble cortisone (dexamethasone sodium) is washed out of the eye within approximately 24h after a single intravitreal injection, the use of triamcinolone acetonide (TA) which as a crystalline steroid has a considerably longer absorption time[1-3]. Recently intravitreal TA (IVTA) has been applied for treatment of intraocular proliferative, edematous and neovascular diseases[3].

It is known that steroids cause vasoconstriction through the specific receptors located on the vascular endothelium and the vascular smooth muscle cells [4]. They decrease vascular permeability by causing hypertrophy of smooth muscle cells

and also increase peripheral vascular resistance by causing perivascular fibrosis [4]. Some studies in the literature had shown that systemic, subtenon and topical steroids may cause changes in ocular blood flow [5-9]. In the literature has been shown that intravitreal steroids may cause changes in ocular blood flow[10,11].

In this study, using Color Doppler Ultrasonography (CDU), we evaluated the effect of an injection of 4 mg/ 0.1 mL IVTA on ocular blood flow.

SUBJECTS AND METHODS

This prospective study includes 46 IVTA injected patients: 22 eyes for diabetic macular edema (DME), 12 for central retinal vein occlusion (CRVO) and 12 for choroidal neovascular membrane (CNVM). After the local ethics committee approval, informed consent from patients was included. This study was conducted in accordance with the declaration of Helsinki.

All patients underwent a detailed ophthalmological examination. Best corrected visual acuity was determined with Snellen charts, whereas intraocular pressure was measured with a Goldman applanation tonometer. A detailed fundus examination was performed after pupillary dilatation with tropicamide.

All patients with DME had type 2 diabetes mellitus (DM). DME diagnosed with fundus examination, Fundus florescein angiography was used when needed. Patients with proliferative diabetic retinopathy were excluded from the study. CRVO was unilateral in all patients and none of the CRVO cases was ischemic, and the mean duration of the symptoms before IVTA injection was 2.3mo (2-3mo). Patients whose CRVO lasted more than 3mo were excluded from the study.

Diagnosis, localization and the dimensions of the CNVM were determined by FA. These patients were treated with a séance photodynamic therapy (PDT) in accordance with TAP procedure [12]. Twenty-four hours after the PDT, all of these patients were injected with IVTA.

All intravitreal injections were performed in sterile conditions in the operating room. After topical anesthesia with proparacaine hydrochloride, the inferior and superior fornices were cleaned with 5% povidone iodine. We drained from the Kenacort-A (40 mg/mL, Bristol Myerss, Squibb Co, Princeton, NY, USA) 4 mg/0.1 mL and injected it into the central vitreous cavity, 4 mm away from the limbus on the inferotemporal area of the globe, with a 27 gauge syringe. All patients were advised not to lie down for 2h in order to prevent the triamcinolone particles from falling onto the fovea. All patients were prescribed topical antibiotics to be taken 4 times a day for 1wk.

The analysis of ocular blood flow of the patients who were injected IVTA was measured by the same radiologist, using the CDU method with the same machine (Logic 9; GE, USA) with 9-12 MHz linear probe. The ocular blood flow of both eyes in the patients of the study group was measured before injection, at the end of the first week and at the end of the first month visit whereas. After controlling the systemic hypertension, the patients lied on supine position and the measurements were performed through closed eyes without any compression to the globe. The Doppler spectrum of ophthalmic artery (OA) was obtained where it crosses the optic nerve, of the central retinal artery (CRA) from the surface of the optic nerve and of the lateral branches of posterior ciliary arteries (PCA) 0.3 mm posterior to the optic nerve head. We enrolled the peak systolic velocity (PSV, cm/s), the end diastolic velocity (EDV, cm/s) and the resistivity index (RI) as ocular blood flow parameters of these three arteries. The RI were computed according to the Pourcelot formula [RI=(PSV-EDV)/PSV]. Ocular blood flow was measured before, at the end of the first week and at the end of the first month following IVTA injection.

Table 1 Demographic data of patients $\bar{x} \pm s$

Groups	*n*	Age (min-max)	M/F
Diabetic macular edema	22	60.86±6.52 (54-79)	13/9
Central retinal vein occlusion	12	58.56±10.18 (40-72)	7/5
Choroidal neovascular membrane	12	69.50±5.56 (64-77)	8/4

The patients were evaluated on the first day, at the end of the first week and at the end of the first month after the injection. At each visit, we routinely checked the visual acuity, measured the intraocular pressure, examined with slit lamp biomicroscopy and performed detailed fundus examination. We evaluated the patients with FFA when it was necessary.

We accepted diabetic patients whose HbA1c was above 7 as uncontrolled DM patients and excluded then from the study. Also patients with systemic hypertension above 140/90 were excluded from the study. Also patients for whom a grid laser photocoagulation was performed in a time period shorter than three months before the injection, patients who were using any systemic drugs that may affect the vascular tonus, patients who have vasculitis, glaucoma and previous ocular surgery were excluded from the study.

As statistical analysis we used the SPSS 16.0 for Windows package software (SPSS Inc, Chicago, IL, USA). Repeated measures ANOVA test and Wicoxon test were used for statistical comparisons and a P-value less than 0.05 was accepted as significant statistical difference.

RESULTS

The mean age of 22 DME patients was (mean±SD) 60.86± 6.52 (54-79)y. Thirteen of these patients were men and 9 were women (Table 1). All of these patients had type 2 DM and the duration of DM was 14.6 ±7.9y. In addition, 5 patients had systemic hypertension as well.

In the DME group, PSV of OA at the first of the first month (37.48 ±10.87 cm/s) increased compared to pre-injection

Table 2 Comparison between the values of the ocular blood flow of the diabetic macular edema patients on the first week and the first month after the injection $\bar{x} \pm s$

Ocular blood flow parameters	Preoperative	First week	First month	*P*
Ophthalmic artery				
PSV (cm/s)	31.39±10.84	33.27±9.71	37.48±10.87	0.048[a]
EDV (cm/s)	6.40±3.40	7.14±3.04	7.72±2.78	0.150
RI	0.80±0.08	0.80±0.04	0.80±0.05	0.969
Central retinal artery				
PSV (cm/s)	9.47±3.37	8.69±3.09	7.97±2.67	0.049[a]
EDV (cm/s)	3.04±1.70	2.44±1.0	2.48±0.76	0.150
RI	0.69±0.10	0.70±0.10	0.66±0.09	0.406
Posterior ciliary artery				
PSV (cm/s)	17.95±6.88	20.08±8.55	17.88±8.04	0.969
EDV (cm/s)	4.32±2.0	5.17±2.42	4.83±2.30	0.391
RI	0.73±0.11	0.73±0.08	0.71±0.08	0.497

PSV: Peak systolic velocity; EDV: End diastolic velocity; RI: Resistivity index; [a]*P*<0.05 statistically significant.

Table 3 Comparison between the values of the ocular blood flow of the central retinal vein occlusion patients on the first week and the first month after the injection $\bar{x} \pm s$

Ocular blood flow parameters	Preoperative	First week	First month	*P*
Ophthalmic artery				
PSV (cm/s)	36.14±0.85	34.10±12.61	38.22±12.60	0.456
EDV (cm/s)	6.90±2.02	10.11±5.40	9.61±4.40	0.127
RI	0.69±0.06	0.71±0.09	0.75±0.08	0.082
Central retinal artery				
PSV (cm/s)	9.72±2.87	8.36±2.24	8.82±2.51	0.546
EDV (cm/s)	2.93±1.15	2.55±1.47	2.58±0.54	0.409
RI	0.70±0.05	0.70±0.09	0.69±0.08	0.610
Posterior ciliary artery				
PSV (cm/s)	16.72±6.99	16.63±8.76	15.56±7.50	0.778
EDV (cm/s)	3.80±1.51	4.66±3.11	4.57±2.73	0.446
RI	0.76±0.06	0.72±0.08	0.71±0.07	0.064

PSV: Peak systolic velocity; EDV: End diastolic velocity; RI: Resistivity index; *P*<0.05 statistically significant.

value (31.39 ±10.84 cm/s) (P =0.048). There was a statistically significant decrease (P=0.049) in PSV of CRA at the end of the first month (7.97±2.67 cm/s) compared to the pre-injection (9.47 ±3.37 cm/s). There was not any statistically significant difference on the other parameters in the DME group (Table 2).

Mean age of 12 patients with CRVO was 58.56 ±10.18 (40-72)y. Seven of these patients were men and 5 were women (Table 1). Nine patients had systemic hypertension and 5 had DM. All CRVO cases were unilateral and all of them were non-ischemic. Mean duration of symptoms before IVTA injection were 2.3mo (2-3mo). There was not any statistically significant change in CRVO group at the end of the first week and the first month on the ocular blood flow parameters (Table 3).

Mean age of CNVM patients was 69.70±5.56 (64-77)y. Eight of these patients were men and 4 were women (Table 1). There was not any statistically significant change in CNVM group at the end of the first week and the first month on the ocular blood flow parameters (Table 4).

Before the injections the mean IOP values were 13.71 ± 2.07 mm Hg in DME, 14.12 ±2.64 mm Hg in CRVO and 15.25 ±2.75 mm Hg in CNVM patients. There was no statistically significant difference between these groups (P= 0.187). The mean IOP values of DME and CRVO patients on the first week visit were 15.80±3.54 mm Hg and 17.87± 4.35 mm Hg, respectively. There was an increase in the IOP of these patients compared with the pre-injection values and this increase was statistically significant (P=0.002, P=0.026, respectively). The IOP values of DME and CRVO patients were 14.27±2.10 mm Hg and 15.00±1.09 mm Hg (P=0.099, P=0.564 respectively). There was no statistically significant change between the first week (16.50±1.73 mm Hg) and the first month (15.33 ±2.30 mm Hg) IOP values in CNVM patients (P=0.180, P=0.317).

The IOP was measured above 21 mm Hg in 12 of 46 injected eyes (26%). The patients with an IOP above 21 mm Hg were successfully treated with antiglaucomatous agents

Table 4 Comparison between the values of the ocular blood flow of the CNVM patients on the first week and the first month after the injection $\bar{x} \pm s$

Ocular blood flow parameters	Preoperative	First week	First month	*P*
Ophthalmic artery				
PSV (cm/s)	35.06±9.59	32.30±7.36	31.36±5.87	0.253
EDV (cm/s)	8.20±2.32	6.88±3.11	6.74±2.67	0.061
RI	0.76±0.05	0.79±0.04	0.78±0.06	0.456
Central retinal artery				
PSV (cm/s)	11.10±2.16	7.96±2.28	8.19±2.53	0.182
EDV (cm/s)	2.28±0.74	2.08±0.52	1.92±0.67	0.491
RI	0.79±0.06	0.73±0.04	0.74±0.08	0.453
Posterior ciliary artery				
PSV (cm/s)	18.13±6.46	15.05±8.42	15.12±8.20	0.236
EDV (cm/s)	3.81±1.75	4.06±2.65	4.12±2.64	0.663
RI	0.78±0.05	0.73±0.05	0.73±0.05	0.159

PSV: Peak systolic velocity; EDV: End diastolic velocity; RI: Resistivity index; $P<0.05$ statistically significant.

[Dorzolamide 2% (Trusopt®) and/or bimatoprost 0.03% (Lumigan®)]. The IOP was not detected above 21 mm Hg in any patient at the end of the first month. Infectious endophthalmitis, sterile endophthalmitis, pseudohypopion and rhegmatogenous retinal detachment were not seen in any patient during the follow-up period.

DISCUSSION

Some studies in the literature had shown that systemic, subtenon and topical steroids may cause changes in ocular blood flow [5-9]. In the literature has been shown that intravitreal steroids may cause changes in ocular blood flow[10,11]. It is not known how the ocular blood flow is affected by IVTA, however some studies have shown that the distal arterial obstruction increases the PSV of the arteries that supplies the eye[13-15]. TA may affect the ocular blood flow by its vasoconstructive effect on the peripheral arterial resistance[14,15]. Another mechanism may be due to the pass of TA in the retrobulbar area. Injected IVTA should pass through the sclera to the retrobulbar area to have an effect in the retrobulbar area[16,17].

Cekiç *et al*[10] similar to the results of this study reported that the EDV of PCA of the injected eyes decreased at the end of the first month and returned to normal values at the end of the third month after the IVTA injection.

It has been reported that before development of macular edema in diabetic retinopathy, diameter-response anomalies and loss of vascular tonus were observed in retinal arterioles[18]. Also it has been reported that DME decreased after focal laser treatment, however the diameter response in the arterioles supplying this area did not change [19,20]. This information may explain why the RI was not affected after IVTA injection in our study.

There was no any significant change in the ocular blood flow during the follow-up period in the sound eyes of the CRVO patients compared with the fellow eyes. Cekiç *et al*[10] observed increment in the PSV of the CRA at the end of the first week and at the end of the first month, and increment in the RI of the CRA at the end of the first month after IVTA injection in the retinal vein occlusion patients. The PCA and the CRA blood flow values turned to normal at the end of the third month. The researchers thought that these transient changes may be due to the regular decrement of the intravitreal concentration of the TA or due to the autoregulatory mechanisms of the choroid.

Türkçüoğlu *et al*[21] in their study using CDU showed that after PDT; the PCA, PSV and RI values were increased at the end of the first week and turned to normal values at the end of the first month. Cekiç *et al*[11] did not find any change in the hemodynamic parameters in the eyes of patients treated with PDT combined with intravitreal triamcinolone. In accordance with this study, the present study did not find any change in the hemodynamic parameters in the CNVM group. The small number of the patients in CRVO and CNVM may affected this result. Additionally microvascular pathology in diabetic retinopathy can affect whole body vessels. A drug that affects vascular tonus can affect more in eyes with diabetic retinopathy then with the other pathologies. For this reason clinician should keep this in mind when prescribing medicines in patients with diabetic retinopathy. It can be an another subject of study how these alterations in ocular blood flow affect the prognosis of the disease and prognosis of vision.

One of the limitations of this study is the difference between the sample sizes of DME, CRVO and CNVM patients. This difference is because in our clinical practice and also in literature the number of DME patients exceeds the number of CRVO and CNVM patients.

In conclusion, this study shows that 4 mg/0.1 mL of TA has the increased PSV of OA and decreased the PSV CRA in the DME patients. The difference is very close to 0.05

significance level and increased number of the subjects may change the results. It has no effect on the ocular blood flow values of the CRVO and CNVM patients.

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