·Clinical Research·

Changes of intraocular pressure after intravitreal injection of 4mg triamcinolone acetonide in treatment of macular edema

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Abstract

• AIM: To investigate the changes of intraocular pressure (IOP) and associated factors of IOP elevation after 4mg intravitreal injection of triamcinolone acetonide (IVTA) in treatment of macular edema.

• METHODS: The study is prospective, consecutive, and non-comparative interventional case series including 93 eyes with macular edema associated with retinal vein occlusion (n=54 eyes) or diabetic retinopathy (n=39 eyes), which received 4mg IVTA injection. The change in IOP was followed for all cases at pre-operation and 14 days, 1, 2, 3, 4, 5, and 6 months post-operation. Associated factors of IOP elevation were examined regarding baseline IOP, causal disease, age and gender.

• RESULTS: IOP increased significantly (P<0.001) at 14 days 16.02± 2.45mmHg after injection and peaked at 18.80± 6.20mmHg at 2 months post-injection (P <0.001) from 14.85± 2.55 mmHg preoperatively. An IOP rise to the value higher than 21mmHg was observed in 2 (2.2%) eyes 14 days after injection and which was observed in 14 (15.1%), 18 (19.5%), 9(9.6%), 4(4.3%), 0, and 0 eyes respectively at 1, 2, 3, 4, 5, and 6 months after injection. One eye (1.07%) showed pressure elevation of over 5mmHg than baseline 14 days after injection and IOP peaked to 22mmHg (23.7%) at 2 months after injection. Five (5.3%) eyes had an increase of 10mmHg at 1 month and IOP peaked to 12mmHg (12.9%) at 2 months after injection. The rise in IOP was statistically associated with younger age (correlation coefficient -0.18--0.29, P<0.05), high baseline IOP (correlation coefficient 0.52-0.79, all P <0.001), and the presence of diabetes mellitus (correlation coefficient 0.23, P <0.001) but independent of gender (correlation coefficient -0.002-0.04, all P>0.05). In all eyes, IOP could be lowered to the normal range with topical medication, without development of glaucomatous optic nerve head changes.

• CONCLUSION: Elevated IOP after 4mg IVTA injection is common and patients should be monitored beyond 6 months post-injection. In all the cases, IOP can be normalized by topical medication. Patients with high baseline IOP, diabetic retinopathy, and younger age should be carefully monitored for an elevated IOP.

• KEYWORDS: intraocular pressure; intravitreal injections; triamcinolone acetonide; complication

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INTRODUCTION

Macular edema is one of the leading causes for impaired vision in some retinal vascular disorders. Recent clinical studies suggest that intravitreal injection of triamcinolone acetonide (IVTA) may be a therapeutic option for the treatment of macular edema[1-14]. Reduction of central macular thickness and improvement in visual acuity were seen after the injection[4,13]. However, a sustained and severe elevation of IOP is a clinically important issue of intravitreal corticosteroid injections[15,16]. The purposes of this study were to investigate the serial changes of intraocular pressure after intravitreal injections of 4mg triamcinolone acetonide in the treatment of macular edema and the factors that influence these changes.

PATIENTS AND METHODS

This study was designed as a prospective interventional one including 87 patients (93 eyes) who received 4mg/0.1mL (40g/L) IVTA for macular edema at the Department of Ophthalmology, the Fourth Hospital of Xi'an city, People's Republic of China, between January and December 2005. All patients were fully informed about the experimental

characters of the treatment, and informed consent was obtained from each patient. The ethical committee of the hospital approved the study.

The injection was carried out under topical anesthesia. Aided by an operation microscope, a paralimbal paracentesis procedure was performed to decrease the volume of the globe, and 40g/L of triamcinolone acetonide was injected transconjunctivally at 6 o'clock through the pars plana, 4mm post-limbus in phakics and 3.5mm post-limbus in pseudophakics, with a 30-gauge needle attached to a tuberculin syringe. Indirect ophthalmoscope was used to confirm proper intravitreal locations of the suspension and perfusion of the optic nerve head.

The IOP was measured with a non-contact applanation tonometer (Nidek, Gamagori, Aichi, Japan). Three IOP measurements were made in each eye, the mean of which was used for the statistical analysis. IOP was determined before the injection and at intervals of 14 days, 1, 2, 3, 4, 5, and 6 months after the injection. As part of their evaluation, each patient underwent distance visual acuity measurement, general ophthalmic examination including slit-lamp biomicroscopy, and indirect ophthalmoscopy.

It was unnecessary to treat the eye when the postoperative IOP level was under 24mmHg. But when the level ranged between 25 and 40mmHg, the eye should be treated by topical antiglaucoma medications; when the level was above 40mmHg, the eye should be treated by topical antiglaucoma medications and oral with/without intravenous antiglaucoma medications; if it was difficult to control the IOP to normal range by antiglaucoma medications, the eye should be treated by antiglaucoma operation.

Statistical Analysis Descriptive data were collected on each patient including age, gender, and diagnosis. The results were expressed as mean and standard deviation (SD). Gender and diagnosis were expressed as dumb variables. Statistical analysis was performed through SPSS statistical software (version 11.0; SPSS, Chicago, IL). A difference was considered statistically significant when the P value was less than 0.05.

Paired t tests were used to assess the statistical significance of differences in the IOP before and after IVTA. A multiple line regression test was employed to analyze the relationship between the IOP post-operation and the baseline IOP, age, gender, and underlying disease.

RESULTS

Of the 93 eyes, 41 were from women and 52 were from men; the mean age was 59.8±10.8 years. Reason for the IVTA was progressive declining of visual acuity due to macular edema associated with retinal vein occlusion (54 eyes), or diabetic retinopathy (39 eyes).

Table 1 Intraocular pressure (mean±SD) before and after the intravitreal injection of 4mg triamcinolone acetonide; *P* value: difference between the postoperative value and the preoperative value

	Number of eyes	IOP(mmHg)	*P*
Pre-op	93	14.85±2.55	<0.001
14d post-op	93	16.02±2.45	<0.001
1mo post-op	93	17.63±5.98	<0.001
2mo post-op	93	18.80±6.20	<0.001
3mo post-op	93	16.99±4.11	<0.001
4mo post-op	93	16.25±2.41	<0.001
5mo post-op	93	15.67±2.22	<0.001
6mo post-op	93	15.63±1.90	<0.001

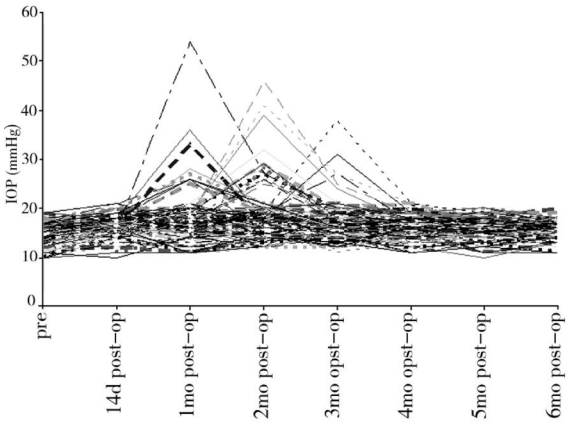

Figure 1 Scatter plot showing the distribution of individual intraocular pressure measurements before and after the intravitreal injection of 4mg triamcinolone acetonide

IOP increased significantly (P<0.001) from 14.85±2.55mmHg preoperatively to a mean maximum of 18.80 ±6.20mmHg postoperatively. The average IOP rose by 7.8%, 18.7%, 26.6%, 14.4%, 7.3%, 5.5% and 5.2% from baseline at 14 days, 1, 2, 3, 4, 5 and 6 months after the injection respectively. The differences of the IOP measurements between pre-and post-operative examinations were significant (all P<0.05, Table 1).

The maximum of IOP after the operation was 54mmHg. The elevation of IOP usually occurred after about 1-2 months (Figure 1).

A rise in IOP to values higher than 21mmHg was observed in 2 (2.2%) eyes 14 days after injection. The peak was reached in 2 months after injection, which was 18mmHg (19.4%). Within 2 months after IVTA, 22 eyes (23.7%) demonstrated an increase in IOP of 5mmHg or greater, and 12 eyes (12.9%) had an increase in IOP of 10mmHg or greater (Table 2).

The greatest increase of IOP above baseline was 37mmHg.

Table 2 The number of eyes with IOP elevation above baseline in each interval after the intravitreal injection of 4mg triamcinolone acetonide

	14d	1mo	2mo	3mo	4mo	5mo	6mo
IOP≥21mmHg	2	14	18	9	4	0	0
IOP rise≥5mm Hg	1	15	22	11	2	0	0
IOP rise≥10mm Hg	0	5	12	2	0	0	0

Table 3 The relationship between the level of IOP at different intervals after the intravitreal injection of 4mg triamcinolone acetonide and baseline IOP, sex, presence of diabetes, age by multiple line regression analysis. The results were showed as the correlation coefficient (*P* value)

Follow-up time	Baseline IOP	Sex	Presence of diabetes	Age
14d	0.53(<0.001)	-0.002(0.43)	0.00(0.49)	-0.08(0.21)
1mo	0.52(<0.001)	0.04(0.43)	0.23(0.01)	-0.18(0.04)
2mo	0.52(<0.001)	0.03(0.37)	-0.09(0.19)	-0.23(0.02)
3mo	0.61(<0.001)	-0.08(0.22)	-0.05(0.31)	-0.29(<0.001)
4mo	0.73(<0.001)	-0.03(0.36)	-0.14(0.09)	-0.25(<0.001)
5mo	0.76(<0.001)	-0.01(0.45)	0.03(0.39)	-0.11(0.15)
6mo	0.79(<0.001)	-0.04(0.34)	0.04(0.36)	-0.21(0.02)

Among the 93 eyes, 8 had received bi-injections and 2 had received tri-injections. Those eyes which developed secondary IOP elevation after the first IVTA had also shown a rise in IOP after two or three intravitreal injections. Those eyes without IOP elevation after the first injection did not develop increased IOP after a second and a third injection.

Among the patients with a postoperative rise of IOP, the IOP could be lowered to normal levels with antiglaucoma medications in all eyes, and no one needed to be treated by penetrating glaucoma surgery, without developing glaucomatous optic nerve head changes. The mean medication-taken duration was 19.5 days (range 12-45 days). The post-injection level of IOP was statistically independent of sex (correlation coefficient range -0.002-0.04, all P>0.05), but significantly associated with the level of baseline IOP (correlation coefficient range 0.52-0.79, all P<0.001) and the presence of diabetes mellitus (correlation coefficient 0.23, P =0.01). It was significantly and negatively associated with the age (correlation coefficient range -0.11- -0.29, all P<0.05, Table 3).

DISCUSSION

Macular edema is the major cause of decreased visual acuity in diabetic retinopathy and retinal vein occlusion. A damaged blood-retinal barrier due to capillary leakage can cause macular edema. Corticosteroids have long been known to tighten up blood vessels resulting in a decrease of vessel leakage. Triamcinolone acetonide was demonstrated to reduce the breakdown of blood-retinal barrier after intravitreal application [17] and was used to treat macular edema secondary to retinal vein occlusion [3-5,12] and diabetic retinopathy [1,2,7-10,11-14] by means of anti-inflammatory and blood-retinal barrier stabilizing effects[17-20].

The results of the present study showed that IOP was 14.85± 2.55mmHg preoperatively, which was similar to the results reported by others [10, 17, 21]. After injecting 8mg IVTA, the level of IOP increased significantly (all P<0.001). The values of IOP were 16.02±2.45mmHg, 17.63±5.98mmHg, 18.80 ±6.20mmHg, 16.99 ±4.11mmHg, 16.8 ±2.41mmHg, 15.67±2.22mmHg and 15.63±1.90mmHg at 14 days, 1, 2, 3, 4, 5, and 6 months after injection respectively. Others [17] reported similar results regardless of the dosage used. In a prospective interventional study conducted by Ozkiris *et al*[17], 212 eyes of 180 patients received 8mg intravitreal injection of triamcinolone, the level of IOP was measured at 1, 3, 6, and 9 months after injection, and the values of IOP were about 17, 20, 16, and 15mmHg respectively.

There may be a delay in the onset of IOP elevation of up to several months after corticosteroid injections [7,15]. In the study of Smithen *et al*[15], ocular hypertension was seen after 4mg IVTA at a mean of 100.6 days (SD 83.1 days). Jonas *et al*[6] have also reported the IOP responded to intravitreal injection of 8mg triamcinolone acetonide. In this retrospective review of 75 eyes of 71 patients, 52% of eyes experienced a pressure elevation higher than 21mmHg with the rise occurring at a mean of 2 months. In our study, the elevation of intraocular pressure was seen at 14 days and peaked at 2 months after IVTA.

When topical corticosteroid testing was performed in diabetic patients, those with no proliferative retinopathy demonstrated a significantly higher incidence of IOP increase than non-diabetic control[19]. The series of Irooka *et al* [20], consisting of 43 patients receiving a single trans-Tenon retrobulbar injection of 20mg triamcinolone acetonide, showed that the presence of diabetes was significantly associated with the increase of IOP after injection (Odds ratio 32.78, 95% confidence interval 2.76-389.24, P=0.006). In our study, we also found that the presence of diabetes would influence the level of IOP post-injection. It is not known whether the responses that were seen in these diabetic subjects were genetically determined or merely modified by ocular complications or other vascular, metabolic, or endocrine changes in the diabetes [20].

Ohji *et al* [21] reported a high incidence of elevated IOP in children less than 10 years of age after instillation of corticosteroids. Jonas *et al* [6] also found that younger age

was a risk factor of IOP elevation after IVTA. In our study, age appeared to be negatively and significantly associated with IOP level after IVTA. It means that ocular hypertensive response to IVTA may occur frequently in young patients.

Compared with others' reports, we got a different finding about the rate of IOP elevation above 21mmHg post injection, which was about 50% in a study by Jonas *et al*[6] and contrasted with about 19.35% peaking in ours. This difference may have been related to the different analysis method. Because the rate in Jonas' study represented the total number of patients who encountered an IOP elevation higher than 21mmHg during the whole follow-up time, but that in our study only represented the number of patients at a given follow-up time point such as 2 months after injection.

It is reported that a significant rise in the serum concentration of corticosteroids was not detected after an intravitreal injection of even high-dose (20-25mg) triamcinolone acetonide [22], so it seems feasible to inject triamcinolone acetonide to diabetic patients.

From a clinical point of view it may be important that in all eyes, the IOP could be controlled by topical antiglaucomatous treatment, meaning that it is feasible to inject triamcinolone acetonide to vitreous.

In conclusion, the findings of our study suggest that the IVTA in a dosage of 4mg could lead to a secondary ocular hypertension; that the rise of IOP may persist at least 6 months after the injection; that the rise of IOP can usually be controlled by topical antiglaucomatous medication; and that the steroid induced ocular hypertension may thus not be a major contraindication against the use of intravitreal triamcinolone acetonide as treatment trial of macular edema owing to diabetic retinopathy and retinal vein occlusion.

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