Intraocular Pressure Elevation after Intravitreal Triamcinolone Acetonide Injection

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Purpose: This study investigated firstly the change of intraocular pressure (IOP) after injection of intravitreal triamcinolone acetonide (IVTA) for the treatment of macular edema and secondly the factors that influence these changes.

Methods: A prospective, non-comparative study was performed in 60 patients at Kangnam Sacred Heart Hospital from October 2003 to September 2004. All the patients received 4-mg IVTA injection.

Results: Mean IOP was elevated from the day after injection and peaked at 20.5 mmHg after 2 months (p=0.000). Twenty-six eyes (43.3%) showed significant IOP elevation. IOP was not controlled despite full glaucoma medication in 7 (11.7%) eyes. Two eyes underwent filtering surgery. Younger age was a statistically significant predictive factor for IOP elevation (p=0.009).

Conclusions: In this study, patients who needed filtering surgery developed an IOP spike within one week after the injection. Therefore, clinicians should consider checking IOP at the end of the first week. Furthermore, greater cautions is mandatory with relatively younger patients. *Korean Journal of Ophthalmology 19(2):122-127, 2005*

Key Words: Intravitreal triamcinolone acetonide (IVTA) injection, Intraocular pressure (IOP), Younger age

Intravitreal steroid injection has been widely used in the field of ophthalmology since intravitreal dexamethasone injection was first performed for the treatment of endophthalmitis by Graham and associates in 1974.[1] Among steroids, triamcinolone acetonide is hydrophobic so that its vitreous level can be maintained for up to 3 months.[2,3] In addition, its fibroblast growth inhibition effect is 21-fold more forceful than that of dexamethasone. Consequently, the range of its usage has widened to include intraocular neovascular diseases such as exudative age-related macular degeneration,[4-6] macular edema secondary to diabetes mellitus,[7-9] retinal vein occlusion,[10,11] uveitis[12-14] and pseudophakia.[15-16]

Many studies have investigated increased intraocular pressure (IOP) due to systemic or topical steroid medication for the treatment of intraocular diseases and the risk factors and patterns of IOP elevation are well documented.[17] IOP elevation after intravitreal triamcinolone acetonide (IVTA) injection is also a commonly known complication,[18-26] but studies on the incidence, level of elevation, and risk factors have not been comprehensive. The purpose of this study was to ascertain the pattern of IOP elevation after IVTA injection and the associated risk factors in patients with increased IOP.

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Materials and Methods

A prospective, non-comparative study was performed with 60 patients (60 eyes) who received 4-mg IVTA injection and who were followed-up for a minimum of 3 months at the Department of Ophthalmology, Kangnam Sacred Heart Hospital, College of Medicine, Hallym University, from October 2003 to September 2004. Patients using steroid eye drops or systemic steroid, those previously treated with subconjunctival or subtenon steroid injection, and those with a history of glaucoma were excluded from the study. Reasons for IVTA were macular edema secondary to diabetes mellitus (n=24 eyes, 40.0%), retinal venous occlusion (BRVO or CRVO; n=23 eyes, 38.3%), pseudophakia (n=1 eye, 1.7%), subfoveal choroidal neovascularization (CNV) secondary to age related macular degeneration (ARMD; n=5 eyes, 8.3%) and others (n=7 eyes, 11.7%).

The procedure was administered with topical anesthesia. After sterilization of the periocular area with 5% povidone iodine, 4 mg triamcinolone acetonide was injected with a 26 G needle at the inferonasal or inferotemporal site, 3.5 mm from the limbus. Paracentesis was not performed. Patients

were maintained in upright position for 24 hours after IVTA injection and antibiotic topical medication (levofloxacin) was administered 4 times per day for 1-2 weeks.

Each patient's IOP was evaluated before the injection,[1,7] and 14 days after the injection, and monthly afterwards using a noncontact tonometer (TOPCON CT-80). Mean IOP of three measurement was used, and when the measured pressure by the noncontact tonometer was over 21 mmHg, IOP was remeasured with Goldman applanation tonometer to reduce errors. A significant IOP elevation was defined as IOP >21 mmHg or a rise of more than 5 mmHg in patients with IOP over 21 mmHg on their first examination. Correlations with age, sex, underlying diabetes mellitus or hypertension, refractive error, and previous ophthalmologic operation history were also analyzed to investigate the factors related to IOP elevation.

Independent-samples T-test and chi-square test were performed using SPSS version 10.1 for statistical analysis.

Results

The median follow-up period was 6.1 months (range 3-11 months), and the 60 patients consisted of 30 men and 30 women. Mean age was 57.3 years (range 24-80 years) and refractive errors ranged between -7.75 diopters and +3.25 diopters (mean 0.35 diopters). The mean IOP was slowly elevated from the day after the treatment, peaked at 20.5 mmHg at 2 months after injection and was then reduced. From the 14th day (mean IOP=18.4 mmHg, p=0.001) to the 3rd month (mean IOP=19.1 mmHg, p=0.000) after the IVTA injection, IOP was significantly increased compared to preoperative states (Table 1). Twenty-six (43.3%) of the 60 eyes presented a meaningful increase of IOP, and topical or systemic glaucoma medication had to be administered to these 26 eyes to control IOP. To determine the factors that influence IOP elevation, the patients were classified into two groups: normal IOP (Group A, n=34 eyes) and increased IOP (Group B, n=26 eyes), during the follow-up period. The mean IOP of Group A and Group B during the follow-up period is shown in Fig. 1. Seven (11.7%) of 26 eyes in Group B showed IOP raised above 30 mmHg for over 2 months despite administration of topical or systemic glaucoma medication (Fig. 2). Among these seven eyes, two (a,b) recovered to normal IOP range during the long term follow-up period, and two patients (c,d) were lost during the follow-up period and further observation was not available. Two eyes (e.f)(3.3%) showed persistent ocular hypertension despite full glaucoma medication and required filtering surgery to control IOP. After conventional penetrating glaucoma surgery, IOP was normalization. In the last eye (g), even though topical glaucoma medication was administered due to IOP elevation, IOP fluctuation continued for several months and the patient was still being followed-up at the time of writing.

The relation of each factor to the elevation of IOP was evaluated (Table 2). Post-injection elevation of IOP was statistically independent of sex (p=0.602), diabetes mellitus (p=0.651) hypertension (p=0.171), refractive error (p=0.117) and previous vitrectomy history (p=0.208), but was dependent on younger age (p=0.003; mean age: Group A=61 years vs. Group B=53 years). However, those with previous cataract operation history (p=0.020) had a statistically significant relation with normal IOP (Table 2).

Eight patients (8 eyes) received second injections (13.3%), including 4 with diabetic macular edema and 4 with macular edema due to venous occlusion. The mean interval between the first and second injection was 4.88 months. Except one eye, all eyes experience elevated IOP at the first or second IVTA injection. All eyes which developed a secondary ocular hypertension after a second IVTA injection had also previously shown elevated IOP after the first IVTA injection.

Table 1. Intraocular pressure (IOP) before and after 4-mg intravitreal triamcinolone acetonide injection

Follow up time	Number of eyes	IOP (mmHg)		p-Value
		Mean	Range	
Pre-injection	59	14.6	8~24	
1 day	51	15.3	8~26	0.366
7 days	42	16.6	10~39	0.055
14 days	40	18.4	11~44	0.001
28 days	48	19.0	10~56	0.002
2 months	46	20.5	9~50	0.000
3 months	50	19.1	10~42	0.000
4 months	30	17.0	9~42	0.078
5 months	23	18.5	9~46	0.074
6 months	27	15.5	9~32	0.319
7 months	19	15.4	8~25	0.426
8 months	12	17.2	10~32	0.194
9 months	9	15.3	11~19	0.539
10 months	5	12.2	8~18	0.129
11 months	3	16.3	15~19	0.379

p-value: difference between postoperative and preoperative values

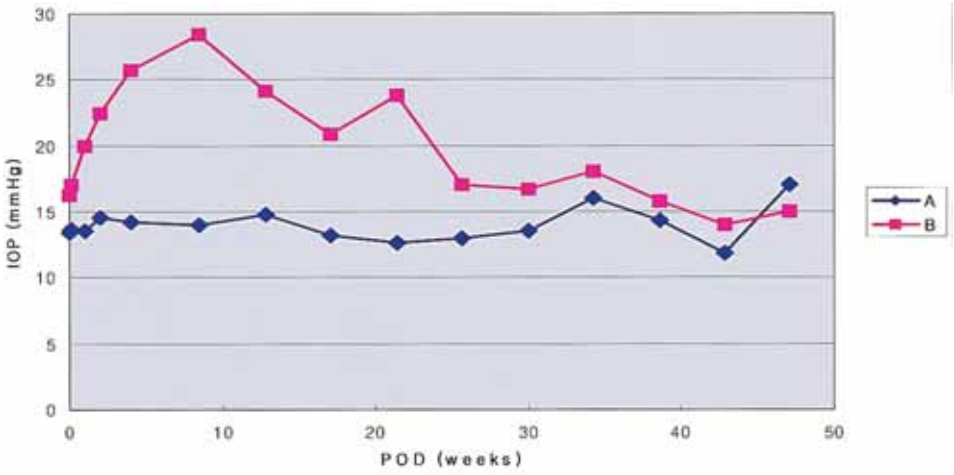

Fig. 1. Distribution of mean intraocular pressure (IOP) after 4-mg intravitreal triamcinolone acetonide injection in 60 patients, 60 eyes. A: group of patients with normal IOP (N=34). B: group of patients with postoperative IOP elevation (N=26).

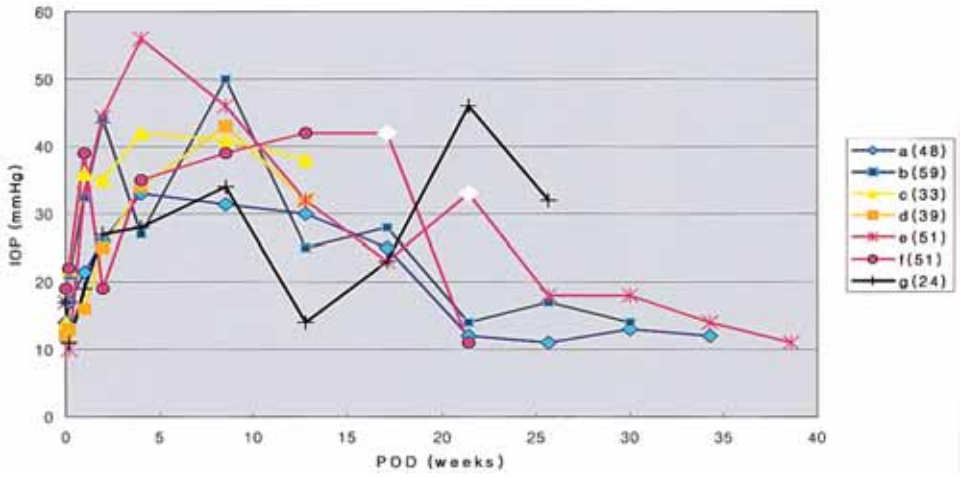

Fig. 2. Distribution of intraocular pressure (IOP) in patients with uncontrolled IOP (N=7). a,b: recovered to normal range of IOP during the long term follow-up period. c,d: were lost during the follow-up period and further observation was not available. e.f: showed persistent ocular hypertension despite full glaucoma medication and required filtering surgery to control IOP. After conventional penetrating glaucoma surgery, IOP was normalization. g: even though topical glaucoma medication was performed due to IOP elevation, IOP fluctuation continued for several months and the patient was still on follow-up at the time of writing.
(number): patients age, ◇: date of trabeculectomy

However, two of the 7 eyes that had shown IOP elevation after the first injection did not develop increased IOP after the second injection. Those eyes without a pressure rise after the first injection did not develop increased IOP after the second injection (Table 3).

During the follow-up period, severe complications such as endophthalmitis, retinal detachment, and vitreous hemorrhage did not occur.[26-31] Because the degree of cataract progression was not recorded consistently, the incidence was not determined, but 3 (5%) of the 60 eyes had to undergo cataract surgery.

Discussion

Corticosteroids are well known for their effectiveness in the inhibition of prostaglandin,[32] inflammatory adhesion molecules such as ICAM-I and MHC-II, growth factors such as vascular endothelial growth factor (VEGF) and in the induction of plasminogen activator inhibitor (PAI)-1. As a result, they tighten up the blood vessels and maintain the integrity of the blood-retinal barrier. Consequently, steroids have been used for the treatment of various ocular diseases, when applied either topically or systemically. However, the eyes account for only 0.01% of the entire body volume, so in order to treat an ocular disease, systemic medication in the place of intraocular direct injection will need a significantly higher dosage to reach the same intraocular concentration, with the consequence of more systemic side effects.

Table 2. Factors affecting intraocular pressure (IOP) elevation

Factors	Group A vs. B
	p-value
Mean Age	0.009*
Sex	0.602
Past Medical History	
Diabetes Mellitus	0.651
Hypertension	0.171
Ophthalmologic operation History	
Phaco. + PCL	0.020†
Vitrectomy	0.208
Mean Refractive Error	0.117

Group A: group of normal IOP during follow-up period (N=34). Group B: group of increased IOP during the follow-up period (N=26). *Younger age showed a statistically significant relation with IOP elevation (p=0.009). †In cases with previous cataract operation history, there was a statistically significant relation with normal IOP (p=0.020).

Therefore, direct intraocular injection of steroid delivers the desired drug to its target tissue in the most direct fashion without extraocular side effects.

Intraocular injections of steroids were first demonstrated 30 years ago, but IVTA injection for the treatment of intraocular neovascular disease and macular edema from various causes has become commonplace only in the last 5 years. Following the reports of good results for IVTA injection, a lot of attention has been focused on its complications.[27-31] Among the complications, procedure- related, adverse events include endophthalmitis, retinal detachment, and vitreous hemorrhage. On the other hand, steroid-related adverse events can also occur, such as elevated IOP, cataract and others. Procedure-related, adverse events are severe complications and can be vision threatening, but their incidence rate is inappreciable, and can be further reduced by the operator's caution. This differs in complications caused by steroids themselves such as IOP elevation and cataract, which have a high incidence rate and are not influenced by the operator's skills.

The results on IOP elevation differ in every report that has investigated the phenomenon. Danis et al. reported IOP elevation in 25% of patients after 4-mg IVTA injection[4] and Kreissig et al. reported IOP elevation in 38.3%.[19] In both reports IOPs were controlled with topical medication. Wingate and Beaumont reported IOP elevation of more than 5 mmHg in 32% of patients after 4-mg IVTA injection and more than 10 mmHg in 11%, and reported that this is in concordance with the 30% steroid responders of the general population.[20] In the report of Bakri and Beer, the result was a little higher, at more than 5-mmHg elevation in 48.8% and more than 10 mmHg in 27.9%.[21] Meanwhile, Jonas et al., reporting IOP elevation in 52% after 25-mg IVTA, stated that in spite of the maximal medical therapy on one eye, IOP was not controlled and filtering surgery was required.[22,23] Likewise, Antcliff et al also performed trabeculectomy on one eye for IOP control after 2-mg IVTA,[12] and Singh et al performed Ahmed valve placement in 3 eyes after 4-mg IVTA.[24] Kaushik et al. performed not only trabeculectomy but also pars plana vitrectomy to eliminate the corticosteroids.[25]

As described above, IOP elevation after IVTA injection is a common and now well-documented side-effect, but with large variation in incident rate. Considering some of the patients whose IOP was not controlled and who had to undergo filtering surgery or vitrectomy, determining the risk factors of IOP elevation and the patterns of increased IOP after IVTA injection will provide considerable help in prescribing the treatment, recommending the injection and observing the follow up. Accordingly, in this study, we investigated the known risk factors of IOP elevation from the usage of systemic or topical steroids. Regarding the difference in the mean elimination half-life of triamcinolone in the vitrectomized eye and the nonvitrectomized patients, we investigated the relations of IOP elevation on the basis of previous ophthalmologic operation history.

Among the risk factors of steroid-induced glaucoma, primary open angle glaucoma (POAG) and first-degree relatives of POAG patients were excluded from this study.

Table 3. Time at elevation of intraocular pressure (IOP) in the patients who underwent intravitreal triamcinolone acetonide injection twice

Patients	Time (POD) at elevation of IOP		Interval between the 1st & 2nd IVTA injection
	1st injection	2nd injection	
1	2 mon	1 mon	6
2	14 days	–	7
3	7 days	7 days	6
4	–	–	6
5	3 mon	2 mon	4
6	2 mon	–	6
7	2 mon	1 mon	2
8	1 day	2 mon	2

There was no IOP elevation in one patient (patient 4). In two cases (patients 2 and 6) IOP elevation occurred after the first injection but not after the second injection. In the other cases, significant IOP elevation occurred after both injections. POD: post-operation days, IOP: intraocular pressure, IVTA: intravitreal triamcinolone acetonide.

We found that other risk factors such as diabetes mellitus, hypertension, and high myopia had no correlation with IOP elevation after IVTA injection. However, IOP elevation was statistically more frequent in the relatively younger group (p=0.009), although age has not been recognized as a risk factor in a steroid responder. Especially, 7 eyes whose IOP was not controlled for more than 2 months despite full glaucoma medication (11.7%) were all of patients under 60 years of age (mean age, 43.6). These results were in concordance with those of Jonas et al's study.[22] Neither our study nor theirs provided a satisfactory explanation of the cause. Additional studies should therefore be performed on this topic. Meanwhile, as in the study by Beer et al, after 4-mg single intravitreal triamcinolone injection, considering that the elimination half life is 1/6 in the vitrectomized patients compared to the nonvitrectomized patients,[2] it can be predicted that in vitrectomized patients, either there will be no IOP elevation, or if there is, it will normalize rapidly. Actually, in this study, 2 eyes with previous vitrectomy history both showed normal IOP. However, this result was not statistically significant, probably because of the insufficient number of cases. Also, in cases with previous cataract operation history, there was a statistically significant relation with normal IOP (p=0.020). This result is in contrast to that of Singh et al., in which all 3 eyes that underwent filtering surgery for the control of IOP were pseudophakic eyes.[24] From these results, it is therefore difficult to say that cataract surgery has a protective effect on the increased IOP after IVTA injection. Further investigation is required.

In this study, 26 of 60 eyes (43.3%) showed elevated IOP. As stated above, trabeculectomy was performed for control of elevated IOP in 2 of the 60 eyes (3.3%). Both patients were 51-years-old males whose IOP was increased rapidly to over 50 mmHg and whose IOP was not controlled despite full glaucoma medication. In one eye, IVTA was injected to treat diabetic macular edema (e), and in the other, to treat macular edema caused by CRVO (f). The two patients shared no other characteristics except age. However, both eyes did show IOP normalization after trabeculectomy and there was no nerve damage. The commencement of IOP elevation in the 26 affected eyes varied from 1 day (3 eyes, 11.5%) to 4 months (1 eye, 3.8%) after the surgery (mean, 33.8 days). Particularly, in the two eyes which needed surgical intervention for the control of elevated IOP, the start of the IOP elevation was comparably earlier than the others; with one eye showing 33 mmHg of IOP on postoperative day 7 and the other 22 mmHg of IOP on postoperative day 1 and 39 mmHg on day 7. This result is in concordance with that report by Singh of the 3 eyes that underwent filtering surgery and all developed an IOP spike on the day after the injection.[24]

A second injection was performed in 8 patients (8 eyes, 13.3%). Identical to the report of Jonas et al,[22] all eyes which developed secondary ocular hypertension after a second IVTA injection had also previously shown elevated IOP after the first IVTA injection. Those eyes without a pressure rise after the first injection did not develop increased IOP after a second injection.

In conclusion, IOP elevation is a common side effect after 4-mg IVTA injection (43.3%) and it usually responds to topical glaucoma medication. However, in some cases IOP was not controlled despite full glaucoma medication, and surgical intervention was required. In this study, patients who needed filtering surgery developed an IOP spike within a week after IVTA injection. Therefore, clinicians should consider checking IOP at one week after triamcinolone injection. Furthermore, more caution is necessary in recommending intravitreal triamcinolone injection to relatively younger patients.

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