The association of intravitreal triamcinolone acetonide and posterior subcapsular cataract development

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The association of intravitreal triamcinolone acetonide and posterior subcapsular cataract development

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Abstract

The association of intravitreal triamcinolone acetonide and posterior subcapsular cataract development

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Intravitreal triamcinolone acetonide(IVTA) is currently used to treat various macular edemas secondary to diabetic retinopathy, branch and central retinal vein occlusion, choroidal neovascularization, and, uveitis, etc.

However, the treatment through pars plana injection and the effects of the corticosteroid entails complications such as retinal detachment, vitreous hemorrhage, increased intraocular pressure, pseudohypopyon, endopthalmitis, and cataract formation. Among these complications, treatment with corticosteroids is generally associated with two common and serious ocular side effects; that being elevated intraocular pressure (IOP) and accelerated cataract formation.

Therefore, this study is to prospectively investigate the development and progression of posterior subcapsular cataract 6 months after the current maximal 25mg intravitreal pars plana triamcinolone injections in one eye of patients with macular edema secondary to diabetes and retinal vein occlusion and its influence on visual acuity.

The prospective interventional case series study included all 38 patients (27 women, 11 men; 76 eyes) who visited the Siloam Eye Hospital's retina clinic with diabetic retinopathy or retinal branched or central vein occlusion from the beginning of March to the end May 2005. The degree of cataract was depicted before IVTA and after IVTA on monthly bases by the same surgeon. Among the 38 treated eyes, there was an increase of cataract degree by 1 grade at the end of 6 months in 10 patients. The types of progressed cataract

were PSC in 7 patients, cortical in 6 patients, and nuclear sclerosis in 1 patient. Four patients had both an increase in grade of PSC and cortical opacities while 6 patients had showed a progression of only one type of cataract.

The development and progression of cataract may mask the vision improving effects of high dose intravitreal triamcinolone acetonide injection in certain cases.

Key words: intravitreal triamcinolone acetonide, posterior subcapsular, nuclear sclerosis, cortical opacity

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I. Introduction

In ophthalmology, corticosteroids have been used since the early 1950s to suppress intraocular inflammation by reducing inflammatory exudation and inhibiting proliferation of fibroblasts and the formation of granulation tissues. There route of administration been given either topically as eye drops; locally by subconjunctival, subtenon, parabulbar, or retrobulbar injections; or systemically as oral medications or intravenous or intramuscular injections.[1]

The successful use of intravitreal triamcinolone acetonide(IVTA) to treat various macular edemas secondary to diabetic retinopathy, branch and central retinal vein occlusion, choroidal neovascularization, and, uveitis, etc. has lead to an increase in its usage during the past few years.[2 3 4 5 6]

Although the exact action of intravitreal triamcinolone acetonide in the treatment of CME has not been well described, several hypotheses on the mechanism of how corticosteroids induce a reduction of macular edema have been proposed. These included a local reduction of inflammatory mediators by the down-regulation of vascular growth factors such as VEGF and anti-inflammatory effects through inhibition of the arachidonic acid pathway and prostaglandin (a known mediator of vascular permeability) production.[7 8 9 10 11]

Also, mechanisms of increased diffusion by the modulation of calcium channels,[12] and improvements in blood-retinal barrier function[13 14 15] may contribute to the healing effects of corticosteroids.

Despite the mechanism of action, the effects of IVTA has been reported to drastically improve retinal thickness and decrease cystic spaces observed by current devices such as optical coherence tomography.[16]

Often, however, the intraocular concentrations of steroids were not high enough to achieve a therapeutic level, or the systemic side effects were too pronounced for a prolonged treatment. In an attempt to overcome this limitation of ocular steroid therapy, Peyman, Machemer, Tano, Ryan, and others suggested the intravitreal application of steroids to locally suppress intraocular inflammation and to reduce cell proliferations.[13 14 17 18]

Because soluble cortisone is cleared out of the eye within 24 hours after injection,[14] crystalline cortisone (triamcinolone acetonide), which remains intravitreally for up to 3 months after the injection was selected.[1] Intraocular delivery of corticosteroids appears to be safe and has the potential to be more efficacious and sustained than other routes of administration.[19]

However, the treatment through pars plana injection and the effects of the corticosteroid entails complications such as retinal detachment, vitreous hemorrhage, increased intraocular pressure, pseudohypopyon, endopthalmitis, and cataract formation.[2 3 4 5 20 21 22] Among these complications, treatment with corticosteroids is generally associated with two common and serious ocular side effects; that being elevated intraocular pressure (IOP) and accelerated cataract formation. [22 23 24]

Studies involving IVTA exhibit a diverse range in the dosage of triamcinolone being injected. The efficacy and related complications of IVTA reported involve the injection dosages from as little as 4mg to as much as 25mg. The reported effects of corticosteroid crystals resulted in decreased macular edema and consequential improvement in vision. However, the vision improving effects have been reported to be temporary.

Because of the catarogenic effects of corticosteroids, the vision reducing effects of progressive cataract, may contribute to visual decrease in cases where the macular edema itself had subsided thus masking the vision improving effects of IVTA.

Therefore, this study is to prospectively investigate the development and progression of posterior subcapsular cataract, the type of cataract associated with the use of steroids, 6 months after the current maximal 25mg intravitreal pars plana triamcinolone injections in one eye of patients with macular edema secondary to diabetes and retinal vein occlusion and its influence on visual acuity.

II. Materials and Methods.

The prospective interventional case series study included all 38 patients (27 women, 11 men; 76 eyes) who visited the Siloam Eye Hospital's retina clinic with diabetic retinopathy or retinal branched or central vein occlusion from the beginning of March to the end May 2005. Both eyes were dilated and they were screened for macular edema and decreased vision.

Since the development of cataract and its subsequent progression is influenced by multiple factors, including age, gender, diabetes, ultraviolet light exposure, smoking, a diet low in antioxidants, and steroid use, intravitreal injections were delivered in one eye of patients with macular edema using the fellow eye as the control. Upon consent of the patient, the degree of cataract was depicted before IVTA and after IVTA on monthly bases by the same surgeon. The system for grading cataracts was according to the internationally recognized Lens Opacities Classification System III.

The IVTA injection technique was similar for all patients. The procedure was done under aseptic conditions in the operation room. A lid speculum was placed between the eyelids. The conjunctiva, eyelids, and eyelashes were disinfected with 10% povidone iodine. Topical 0.5% proparacaine hydrochloride drops (Alcain;Alcon Laboratories, Fort Worth, TX, USA) were then placed on the ocular surface, followed by application of 4% topical lidocaine using a cotton tip pledget over the injection site. Triamcinolone acetonide(40mg/ml; Bristol Myers Squibb Co., New York, NY, USA) was drawn into a 1cc syringe after first cleansing the top of the container with an alcohol wipe. The 1cc syringe was then tape on to the wall needle side up for approximately 3 hours prior to injection so that the white triamcinolone crystals precipitate to the bottom of the syringe. The clear supernatant was discarded leaving only 0.1cc triamcinolone crystals. The remaining 0.05cc was injected via 30-gauge needle 4mm from the limbus in the inferior temporal quadrant in an attempt to minimize frequent symptoms of floaters

during the first few days after the injection. The needle was introduced into the mid-vitreous cavity, aiming towards the posterior and slightly inferiorly with visualization of the needle tip and using a single, continuous maneuver, the triamcinolone acetonide was injected into the eye. The needle was removed simultaneously with the application of a cotton tip over the entry site. Upon confirmation of no scleral leakage, irrigation with topical antibiotic solution and instructions to apply the antibiotic solution six times a day for 1 week was given. Patient was asked to return the next day and weekly for 1 month and monthly thereafter for grading of lens opacification, visual acuity, fundus evaluations, and IOP exams.

The degree of cataract progression was measured as the difference in cataract grade between baseline and the end point (6 months) of the study. Cortical, nuclear and posterior subcapsular (PSC) forms of cataract were graded separately. The progressions of the 3 forms of cataract were then evaluated among the eyes treated with intravitreal triamcinolone and the untreated fellow eyes using the Kaplan-Meier survival analysis and the log-rank test.

III. Results

A total of 38 eyes of 38 patients (27 female and 11 male) received intravitreal injection of 25 mg triamcinolone acetonide. Table 1 shows the baseline demographic data of the patients.

Table 1. Baseline demographic data of patients

Characteristics	Number (%)
Patients	38(100)
Men/Women	11(29)/27(71)
Mean age(yrs)	65.8(SD=6.7)
Diabetic Mellitus (DM)	8(21)
Hypertension (HTN)	7(18)
DM & HTN	20(53)
No DM or HTN	3(0.08)

SD = standard deviation

The mean age of the patients were 65.8 ± 6.7 years and the majority of the patients either had a history of diabetic Mellitus, hypertension, or both. However, there were 3 patients without known medical histories of either of the two.

Table 2 shows the diagnosis of the patient's retinopathy resulting in the decreased vision as well as the visual acuity of both eyes prior to IVTA and at the endpoint (6 months) of the study. Interestingly, among the 3 patients without histories of DM or hypertension, all 3 presented cases of branched retinal vein occlusion.

Table 2. Diagnosed retinopathy, baseline vision, and endpoint vision

Characteristics	Number (%)
CSME	26(68)
BRVO	10(26)
CRVO	1(0.03)
CSME & CRVO	1(0.03)
Baseline Vision	
Control eye	0.37(SD=0.17)
IVTA eye	0.08(SD=0.04)
Endpoint Vision (6 months)	
Control eye	0.37(SD=0.17)
IVTA eye	0.10(SD=0.16)

CSME = clinically significant macular edema
BRVO = branched retinal vein occlusion
CRVO = central retinal vein occlusion
SD = standard deviation.

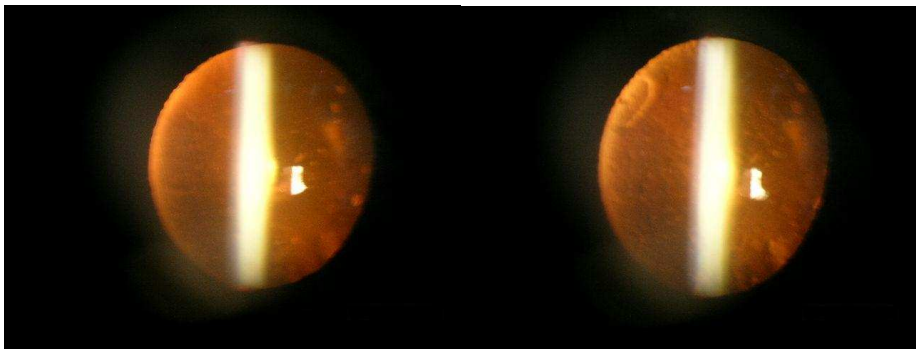
The 38 patients were diagnosed with either diabetic CSME or retinal vein occlusion of the branched or central type. One patient had combined diabetic clinically significant macular edema and central retinal vein occlusion. The vision in the intravitreal triamcinolone acetonide injected eye showed minor but no significant improvement as did the control (fellow) eye at the end of 6 months.

Table 3. Cataract development by 1 or more grades over 6 months

	NS(%)	Cortical(%)	PSC(%)
IVTA treated eyes (n=38)	1(0.03)	6(0.16)	7(0.18)
Control (fellow) eyes (n=38)	0(0)	0(0)	1(0.03)

NS = nuclear sclerosis
PSC= posterior subcapsular

Among the 38 treated eyes, there was an increase of cataract degree by 1 grade at the end of 6 months in 10 patients. The types of progressed cataract were PSC in 7 patients, cortical in 6 patients, and nuclear sclerosis in 1 patient.Table 3 Four patients had both an increase in grade of PSC and cortical opacities while 6 patients had showed a progression of only one type of cataract. Figure I shows 2 examples of cataract(PSC) progression.



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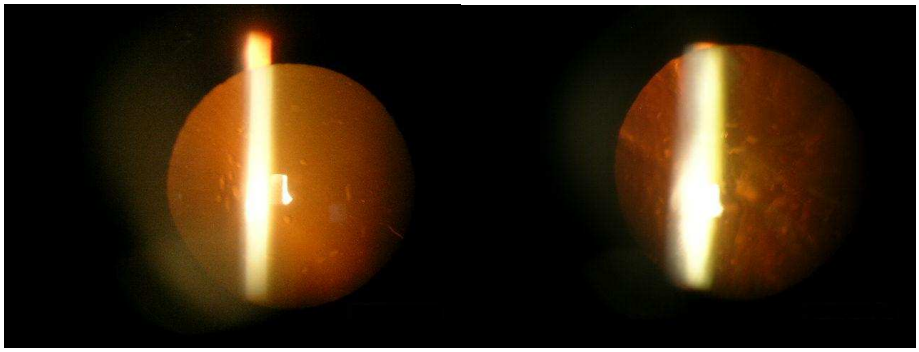
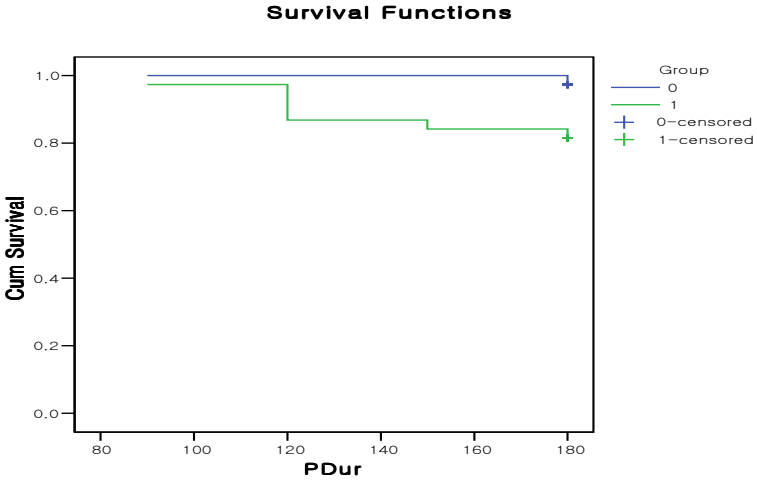


B

Figure 1. Slit lamp retroillumination photo of the progression of PSC in patients (A) and (B). Left photo = pre IVTA, Right photo = post IVTA (6 m)

Of the 10 patients who developed a progression of cataract 3 showed an improvement in vision while 4 sustained equal vision and 3 showed a decrease in vision at the end point (6 months) of the study. Fluorescent angiographic exams of these 10 patients at the month 6 showed residual or recurred macular edema in 3 patients all presenting a decrease in end point vision.

Figure 2 depicts the progression-free survival curves for PSC and cortical cataracts in the eyes intravitreally treated with triamcinolone acetonide. There was a significantly higher rate of progression of PSC ($P<0.0239$) and cortical opacities ($P<0.0112$) in the treated group while the progression of nuclear cataract was not significantly different between the treated eye and the control eye. The earliest cortical and PSC progression began 3 months after IVTA injection occurring in 2 patients. The other 7 patients showed progression in the 4^{th} and 5^{th} month and 1 patient progressed in the final month.



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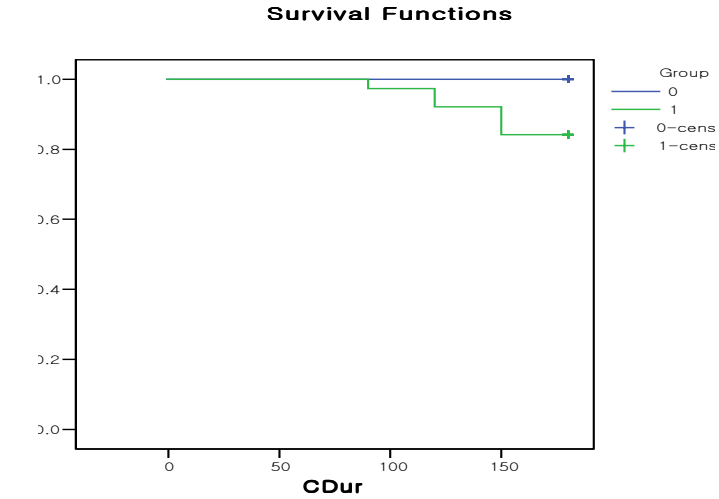

B

Figure 2. Progression-free survival curves for cataracts in IVTA eyes. Time from treatment to progression by 1 or more grade is shown for (A) PSC (log-rank chi-square test, 5.10, 1 degree of freedom; P<0.0239),(B)cortical cataract (long-rank chi-square test, 6.43, 1 degree of freedom; P<0.0112). Dur = days.

IV. Discussion

Intravitreal triamcinolone acetonide is a promising and potentially valuable treatment strategy for select patients with macular edema. The availability of new technologies, especially ocular coherence tomography, has made it possible to document retinal thickness, intraretinal cystic changes, and vitreomacular traction in patients with macular edema. This technology has demonstrated that the anatomical response to treatment with intravitreal triamcinolone is often dramatic and, in many cases, anatomical improvement is associated with improved visual acuity.[3]

Logically, bringing the drug into direct contact with the tissues on which they should act in turn ensures highest localized concentrations and minimal side effects for the rest of the body. Injection triamcinolone acetonide directly into the vitreous indeed achieves this effect but nevertheless accompanies unwanted complications.

Several studies have reported that the most common complication of IVTA treatment was a transient increase in intraocular pressure. In these studies intraocular pressure increased significantly from 15.0 ± 4.2 mm Hg at baseline of the study to a mean maximum of 21.9 ± 7.2 mm Hg and again decreased significantly towards the end of follow-up (9 months) not to differ significantly from baseline.[25] Other studies report that overall, the average intraocular pressure increased by 3.0 mm Hg from the mean of 15.6 mm Hg to 18.6 mm Hg.[7] A brief report of 113 eyes receiving a single 4-mg injection of triamcinolone acetonide found elevation of the IOP by 5 mm Hg or higher in 32% of eyes 3 months after treatment. [22]

The association between systemic steroid use and formation of posterior subcapsular cataract (PSC) was first reported in 1960 by Black et al. Since then, numerous other studies have described an association between cataract and treatment with steroids such as dexamethasone, beclomethasone, prednisone, and triamcinolone, regardless of their route of administration.[26]

In 1963 Valerio first reported the development of PSC after local corticoid use. These opacities are similar in appearance and behavior to those stimulated by systemic glucocorticoid administration.[27]

Although a clear correlation between duration of treatment or dosage and incidence of opacities has not emerged, it appears that the combination of these two variables (duration of treatment and dosage) as well as the route of administration (topical vs. systemic) play roles in the development of steroid-induced cataract.[28]

The cause of steroid-induced cataract seems to be multifactorial. Alterations in the lens metabolism, cellular cation pumps, formation of Schiff base between the C-20 group of the steroid and the ∈-amino group of crystalline lysine residues, and oxidative stress are factors frequently mentioned as contributing to lenticular changes observed in those with cataract.[29 30]

According to the study by Gillies et al, 16 (28.6%) of 56 patients receiving triamcinolone underwent cataract surgery, and 28% required glaucoma medication.[19] Helm and Holland also reported development of significant cataract in 4 (36.4%) of 11 phakic eyes 10 months to 4 years after treatment with triamcinolone injected into the posterior sub-Tenon space in the treatment of intermediate uveitis.[31] Gillies and co-workers report significant progression of cataract in triamcinolone-treated eyes. By the 24 month visit, 8 (24.2%) of 33 triamcinolone-treated eyes had progression by 2 or more Age-Related Eye Disease Study grades(5 progressed by 2 grades, and 3 by 3 grades) compared with 0 of 22 placebo-treated eyes(P=.02). Cataract surgery was performed in 16 (28.6%) of 56 treated eyes of patients who completed at least the 12-month study visit verses 2 (5.0%) of 40 eyes receiving placebo (P=.003). Cataract surgery was performed at a mean of 25 months (12-34) after treatment.[19] Furthermore, the cataractogenic effect of intravitreal triamcinolone acetonide has been evaluated in 144 phakic eyes which consecutively received an intravitreal injection of about 20 mg triamcinolone

acetonide for macular diseases. Re-injections were carried out in 12 (8.3%) eyes. Cataract surgery was performed in 20 eyes 13.9%) 17.4 ± 9.1 months (median, 12.7 months; range, 8.0 to 35.5 months) after the first intravitreal injection. The data may suggest that, in the elderly population of patients with exudative ARMD and other macular diseases, intravitreal high-dosage injections lead to clinically significant cataract with eventual cataract surgery in about 15 to 20% of eyes within about one year after the intravitreal injection.[25]

The present study using a high dosage (25 mg) of IVTA injection for a follow up of 6 months has revealed similar results that out of 38 patients enrolled into the analysis, 10 patients (26.3%) eventually showed a progression of cataract. Among the 3 general types of cataract, not only PSC (7 eyes) but cortical opacities (6 eyes) progressed under the influence of IVTA leaving nuclear sclerosis (1 eye) to be the only type not significantly affected.

Upon scrutinizing the lens for cataract development and cataract progression, certain attributes of PSC formation were also noted. The PSC after IVTA injections generally occupied the polar posterior cortical region starting as small vacuoles and later fusing into linear formations and lesions of opaque clumps. When significantly progressed, the overall morphology of the PSC boundaries were much more circumlinear and the opacities much more evenly distributed compared with those PSC opacities caused by non-steroid factors. Figure 3 The cortical opacities were also somewhat different in that although the progression was from the periphery towards the center, the arrangement seemed to be a less spoke-like than typical cortical opacities.

Oglesby described the PSC which results from corticosteroid therapy as occupying the polar region with sharp borders. He also depicts structures consisting of fine tiny whitish-yellow crystalline opacities separated by equally small vacuoles, together appearing as a granular conglomerate, which occasionally showed linear markings or a few larger vacuoles.[32]

These features are generally consistent with those found in this study and further investigations may lead to more clearly differentiate in the future the characteristics of those cataracts caused by steroids. Although there have been reports that PSC opacities caused by steroid usage partially resolve with time, [33] this study did not find any such resolutions. On the other hand, none of the 10 patients who developed cataract exhibited a decrease in vision enough so as to undergo cataract surgery. This may have been to the relatively short duration of observation.

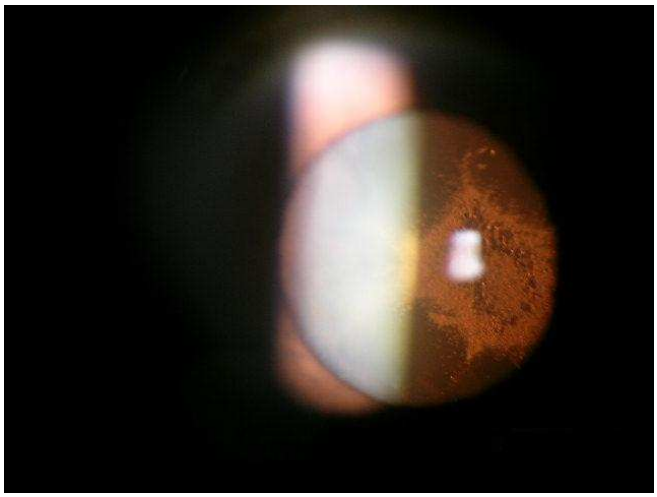

Figure 3. IVTA induced PSC occupying polar area starting as small vacuoles and later fusing into linear formations and lesions of opaque clumps.

V. Conclusion

The injection of triamcinolone acetonide into the vitreous has many proven benefits of prompt resolution of macular edemas caused by various retinopathies and eventual improvement in vision. The resulting dramatic early improvement in vision however, appears to be temporary at best.

Studies show that this improved vision occurring in 23 eyes (92%) by 3.0±2.6 Snellen lines during the following 4 to 6 month time eventually decreased significantly towards the end of the follow up period.[25] There are reports that with a dosage of 4mg, the duration of the effect of intravitreal triamcinolone acetonide as measured by a reduction in macular thickness by optical coherence tomography was less than six months.[3] [34] [35] The effectiveness of steroids in reducing foveal thickening and likely vascular permeability appears to be approximately 5 to 6 months, at which time recurrence of CME became apparent. Recurrence of the CME is thought to be related to inherent damage to the microvasculature from the initial underlying pathology.[7] Jonas et al. agrees with the above studies stating that the duration of an improvement of visual acuity was approximately six to seven months after an intravitreal injection of about 20 mg triamcinolone acetonide in patients with diabetic macular edema.[36]

Since there have been reports of no cataract progression after 2- 4mg injection for 6 months follow up[4] [34] this study injected the current maximal clinical dosage of 25mg triamcinolone acetonide into the vitreous to observe if the vision decreasing effects were caused by the progression of steroid induced cataract.

Of the total 38 eyes injected, no significant difference in visual improvement 6 months following the IVTA injections were found. Among the 10 eyes which developed cataract progression, 3 eyes showed decrease in vision at the end point of the study but this was more so thought to be due to the exacerbation of the macular edema rather that the progression of the

cataract. The 4 patients among the 10 who showed resolved macular edema but did not show an increase of vision may be because of the increase in cataract grade. The development and progression of cataract after IVTA injection has indeed been observed but because vision is a very subjective attribute, a 1 grade increase in cataract that may be disturbing to one person may not be noticeable to another. However, if there is an improvement of macular edema but not an improvement in vision after IVTA injections, the development or progression of cataract may be the reason and with high dosages this may occur as early as 3 months post-injection.

Although the baseline cataract evaluations and all of the IVTA injections were carried out by a single surgeon there may have been subjective variations in grading the degree of cataract according to Lens Opacities Classification System III (LOCS III) and in preparing the 25 mg dosage of triamcinolone acetonide due to the small volume handled. Furthermore, the small number of patients included and the relatively short follow up period of 6 months for the detection of cataract progression are some of the short comings of this study that may be needed to be improved.

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Abstract (in Korean)

유리체내 triamcinolone acetonide 주입과 후낭하형 백내장과의 관계

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유리체내 triamcinolone acetonide 주입술은 당뇨병성망막증, 정맥폐쇄, 노인성 황반증, 포도막염 등으로 인한 황반부종의 치료로 사용되고 있다.

그러나, 스테로이드의 사용은 안압 상승이나 백내장의 발생과 같은 합병증을 유발한다고 알려져 있다.

그러므로, 본 연구는 현재 사용되는 최고용량인 25 mg triamcinolone acetonide 을 당뇨병 또는 망막정맥폐쇄로 인한 황반부종으로 시력저하를 호소하는 환자들의 안구 유리체내 주입 후 6 개월 동안 백내장의 발생과 진행 여부를 관찰하고자 한다.

본 연구는 2005 년 3 월에서 5 월 사이에 황반부종과 시력저하로 실로암안과병원을 찾은 총 38 명의 환자 (27 여자, 11 남자; 76 안)을 대상으로 하였다. 백내장의 정도를 약물 주입 전에 국제공인 방법인 LOC III 로 기록하였고 그 후 첫 1 달은 매주 그리고 그 후는 매달 백내장의 정도를 비교군인 반대 눈과 대조하였다.

유리체내 triamcinolone acetonide 을 주입한 총 38 안중 연구 종료 시점인 6 개월 후 1 단계이상 백내장의 진행을 보인 환자수는 10 명이며 백내장의 유형은 후낭하형이 7, 피질형이 6, 그리고 핵형이 한 명으로 나타났다. 백내장의 유형중 4 명은 후낭하형과 피질형이 동시에 진행하였으며 6 명은 3 중 한가지 형태의 백내장만 진행하는 소견을 보였다.

그러므로 유리체내 triamcinolone acetonide 의 주입은 통계적으로 유의하게 후낭하형과 피질형 백내장의 발생과 진행에 영향을 주며 이런 백내장의 발생은 치료효과인 시력개선의 저하를 경우에 따라 초래할 수도 있다.

핵심되는 말: 유리체내 triamcinolone acetonide, 후낭하형 백내장, 피질형 백내장, 핵형 백내장