Original Article

Comparison of vitrectomized with nonvitrectomized eyes after subtenon injection of triamcinolone acetonide to treat diabetic macular edema: Retrospective comparative Analysis of an interventional case series

Kang Yeun Pak[1,2], Beom Seok Choi[2,3], Sung Who Park[2,3], Ik Soo Byon[2,4], Ji Eun Lee[2,3]

Purpose: Triamcinolone acetonide (TA) is an alternative option for diabetic macular edema thanks to its cost-benefit ratio and unique delivery route. We performed this study to compare vitrectomized with nonvitrectomized eyes treated with subtenon TA injection for diabetic macular edema. **Materials and Methods:** We retrospectively reviewed the medical records of patients who had undergone subtenon TA injection for diabetic macular edema treatment. The patients were divided into two groups: Vitrectomized and nonvitrectomized. Visual acuity and central subfield macular thickness (CSMT) were analyzed before injection, at 1 and 3 months after injection. **Results:** Visual acuity in vitrectomized group improved significantly at 1 month ($P = 0.002$), but this improvement regressed after 3 months. In the nonvitrectomized group, visual acuity did not improve significantly after 1 month, but it did after 3 months ($P = 0.019$). The CSMT decreased significantly in both groups at 1 and 3 months ($P < 0.001$). There were no significant differences between the groups at either 1 or 3 months with regard to either visual improvement or change in CSMT. **Conclusion:** Subtenon TA injection could be an alternative treatment option for diabetic macular edema, both in vitrectomized and in nonvitrectomized eyes. TA seems to take effect earlier and decay faster in vitrectomized eyes.

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Macular edema is an important cause of impaired vision in diabetic individuals.[1] Focal laser therapy,[2,3] anti-vascular endothelial growth factor (VEGF) injection,[4] and intravitreal dexamethasone implant[5] have been widely accepted as effective treatment options for diabetic macular edema (DME). However, focal laser therapy does not improve visual acuity, and anti-VEGF injection and dexamethasone implants are restrictively expensive. Therefore, although the efficacy of subtenon triamcinolone acetonide (TA) to treat DME has not been established in a large randomized trial, it remains an alternative option thanks to its cost-benefit ratio and unique delivery route.

TA can be injected into the subtenon space from where it is delivered into the vitreous through the transscleral pathway.[6,7] As such, there is a low risk of intraocular complications, such as endophthalmitis or retinal detachment.[8] In addition, TA can be used in vitrectomized as well as nonvitrectomized eyes.[9] In a previous study in rabbits, it was shown that vitrectomized eyes differed from nonvitrectomized eyes with regard to the pharmacokinetics of subtenon TA.[10] However, to our knowledge, clinically based information is limited regarding how the pharmacokinetics of TA differs depending on vitreous status.

In the current study, we compared, in a clinical setting, the characteristics of subtenon TA in vitrectomized eyes with those in nonvitrectomized eyes.

Materials and Methods

The current study was a retrospective, interventional, consecutive case series. We conducted a computerized search and retrospectively reviewed the medical records of patients who had been injected with subtenon TA to treat DME. The patients had all been treated between January 2007 and December 2013 and had been followed up for 3 months or more. Patients who had a history of treatment for DME (focal laser therapy, intravitreal injection, or vitrectomy) in the 3 months before or after the subtenon injection were excluded from the study. Patients who had vitreous interface abnormalities on optical coherence tomography were also excluded from the study. The Institutional Review Board approved the study protocol, and the protocol complied with the tenets of the Declaration of Helsinki.

Subtenon TA injection was performed aseptically under a microscope. After topical anesthesia was induced using 0.5%

[1]Department of Ophthalmology, Haeundae Paik Hospital, Inje University, [2]Department of Ophthalmology, School of Medicine, Pusan National University, [3]Biomedical Research Institute, Pusan National University Hospital, Busan, [4]Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, South Korea

Correspondence to: Prof. Sung Who Park, Pusan National University Hospital, 1-10 Ami-Dong, Seo-gu, Busan, South Korea. E-mail: oph97@naver.com

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proparacaine, a 5% povidone-iodine solution was instilled. A small incision was made at the superotemporal quadrant of the conjunctival fornix, and 40 mg TA (Tamceton™; Hanall Biopharma, Seoul, Korea) was injected using a 25-gauge curved-tip cannula. All patients were then prescribed 0.5% levofloxacin eye drops for 5 days.

The patients were divided into two groups: the "vitrectomized" group and the "nonvitrectomized" group. The following baseline characteristics of each group were recorded: Age, sex, lens status (phakic/pseudophakic), previous number of intravitreal injections, previous history of pan-retinal photocoagulation (PRP), visual acuity, central subfield macular thickness (CSMT), intraocular pressure (IOP), and number of antiglaucoma drugs prescribed. In "vitrectomized" group, indications and methods for vitrectomy were also investigated. Visual acuity, CSMT, IOP, antiglaucoma medication, and any complication were reviewed at 1 and 3 months after subtenon TA injection. Visual acuity was quantified using lines of Snellen visual acuity and converted to logarithm of the minimum angle of resolution (LogMAR) for statistical analysis. The CSMT was measured at the foveal center using the built-in software of the optical coherence tomography (Cirrus™ OCT; Carl Zeiss Meditec, Dublin, CA, USA).

Standard procedure for vitrectomy

Cataract surgery was performed concurrently in patients who required it. Pars plana vitrectomy was performed using the Constellation or Accurus (Alcon Laboratories, Inc, Fort Worth, TX, USA), sutureless 23-gauge vitrectomy system. The internal limiting membrane (ILM) was peeled using indocyanine green (0.025%) in cases of DME. In cases with lack of laser scarring, endolaser was added.

Statistical analysis was performed using SPSS™ 12.0 (IBM Corporation, New York, USA). Differences between study groups were assessed using Fisher's exact test or the Mann–Whitney U-test. Wilcoxon signed-rank test was used to analyze the change in each group. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Sixty eyes from 44 patients were included in the study –34 eyes in the vitrectomized group and 26 in the nonvitrectomized group. Vitrectomy had been done for DME (17 eyes), epiretinal membrane (11 eyes) and vitreous hemorrhage (6 eyes). The average interval between vitrectomy and first injection for DME was 5.8 ± 4.7 months. The baseline characteristics of each group are summarized in Table 1. There were no significant differences in age, sex, follow-up duration, baseline visual acuity, baseline IOP, baseline CSMT, previous history of PRP, and the number of previous intravitreal injections ($P = 0.166$-0.989, Fisher's exact test, Mann–Whitney U-test). In the vitrectomized group, all 34 (100%) eyes were pseudophakic and 20 eyes (58.8%) had performed ILM peeling, which were a significantly higher proportion than that in the nonvitrectomized group.

Visual outcomes

Visual acuity had improved in the vitrectomized group – from 0.65 ± 0.22 logMAR (Snellen equivalent 20/90) at baseline to 0.57 ± 0.20 logMAR (Snellen equivalent 20/75) at 1 month ($P = 0.002$, Wilcoxon signed-rank test); however, this improvement had regressed to 0.59 ± 0.24 logMAR (Snellen equivalent 20/78) after 3 months ($P = 0.63$, Wilcoxon signed-rank test; Fig. 1a). In contrast, in the nonvitrectomized group, visual acuity had not significantly improved after 1 month – from 0.72 ± 0.40 logMAR (Snellen equivalent 20/105) to 0.66 ± 0.33 logMAR (Snellen equivalent 20/92; $P = 0.130$, Wilcoxon signed-rank test) – however, after 3 months, there had been an improvement to 0.63 ± 0.33 logMAR (Snellen equivalent 20/86; $P = 0.019$, Wilcoxon signed-rank test; Fig. 1b).

There were no statistically significant differences between the groups, at either 1 or 3 months, in terms of visual improvement ($P = 0.126$ and $P = 0.467$, respectively, Mann–Whitney U-test; Table 2).

Central subfield macular thickness

The CSMT in the vitrectomized group had decreased from 453.1 ± 132.3 µm at baseline to 310.6 ± 55.4 µm at 1 month and 304.5 ± 64.3 µm at 3 months [Fig. 2a]. In the nonvitrectomized group, CSMT had decreased from 477.1 ± 149.7 µm at baseline to 346.5 ± 90.1 µm at 1 month and 345.9 ± 74.1 µm at 3 months [Fig. 2b]. In both groups, the CSMT decrease was significant at both 1 and 3 months ($P < 0.001$, Wilcoxon signed-rank test). There were no statistically significant

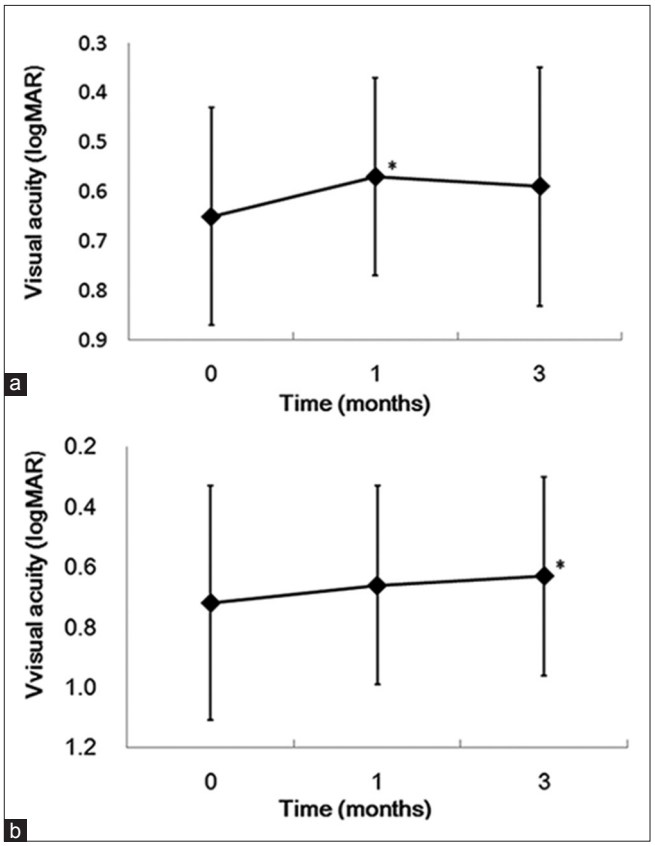

Figure 1: Mean visual acuity values at baseline, and at 1 and 3 months after subtenon triamcinolone acetonide injection to treat diabetic macular edema. (a) Vitrectomized group (b) nonvitrectomized group. Although there was no significant difference in visual improvement between the two groups at 1 and 3 months, there was a significant difference between the groups in the time interval from injection to visual improvement. The vertical lines indicate one standard deviation from the mean (*$P < 0.05$ compared to baseline)

Table 1: Baseline characteristics of patients treated with subtenon triamcinolone acetonide for diabetic macular edema

	Vitrectomized	Nonvitrectomized	*P*
Number of eyes (patients)	34 (26)	26 (18)	
Right/left	19/15	17/9	0.564
Phakic/pseudophakic	0/34	20/6	0.001
Mean age	64.2±8.1	65.0±9.6	0.338
Male/female	11/23	13/13	0.166
Follow-up (months)	22.4±220.2	15.5±8.0	0.287
IOP (mmHg)	14.8±43.5	15.1±53.2	0.687
Visual acuity (LogMAR)	0.65±0.22	0.72±0.39	0.989
Snellen equivalent	20/90	20/105	
CSMT (μm)	453.1±132.3	477.1±149.7	0.479
Previous history of PRP (eyes [%])	34 [100]	25 [96.2]	0.433
Internal limiting membrane peeled (eyes [%])	22 [64.7]	0	<0.001
Number of previous injections	3.5±2.1	3.7±0.99	0.844

Data presented as mean±SD. SD: Standard deviation, IOP: Intraocular pressure, CSMT: Central subfield macular thickness, PRP: Pan-retinal photocoagulation, MAR: Minimum angle of resolution

Table 2: Change in visual acuity, central subfield macular thickness, intraocular pressure, and antiglaucoma drug use after subtenon triamcinolone acetonide injection

	Vitrectomized	Nonvitrectomized	*P*
Visual acuity (LogMAR)*			
1 month	0.08±0.12	0.05±0.16	0.126
3 months	0.06±0.14	0.10±0.18	0.467
CSMT (μm)*			
1 month	-142.6±134.4	-131.2±128.7	0.823
3 months	-148.6±131.3	-131.2±133.9	0.512
IOP (mmHg)*			
1 month	+3.0±3.9	+2.2±3.1	0.848
3 months	+4.0±4.9	+1.9±3.1	0.053
Proportion of antiglaucoma drug users			
1 month	11.8% (4/34)	15.4% (4/26)	0.717
3 months	20.6% (7/34)	19.2% (5/26)	1.00

Data presented as mean±SD. *Changes from baseline value. SD: Standard deviation, CSMT: Central subfield macular thickness, IOP: Intraocular pressure, MAR: Minimum angle of resolution

differences between the groups, either at 1 or 3 months, in terms of CSMT changes ($P = 0.823$ and $P = 0.512$, respectively, Mann–Whitney U-test; Table 2) and CSMT ($P = 0.082$ and $P = 0.055$, respectively, Mann–Whitney U-test).

Intraocular pressure elevation and other ocular complications

IOP had increased by 3.0 ± 3.9 mmHg in the vitrectomized group and by 2.2 ± 3.1 mmHg in the nonvitrectomized group at 1 month. At 3 months, IOP had increased by 4.0 ± 4.9 mmHg in the vitrectomized group and by 1.9 ± 3.1 mmHg in the nonvitrectomized group [Table 2]. There were no statistically significant differences in this regard ($P = 0.848$ and $P = 0.053$ at 1 and 3 months, respectively, Mann–Whitney U-test).

At 1 month, four eyes (11.8%) from the vitrectomized group and four (15.4%) from the nonvitrectomized group used an average of 2.0 antiglaucoma drugs. At 3 months, seven eyes (20.6%) from the vitrectomized group used an average of 2.7 ± 1.1 drugs, and five (19.2%) from the nonvitrectomized group used an average of 2.0 drugs [Table 2]. There were no statistically significant differences in this regard ($P = 0.717$ and $P = 1.00$ at 1 and 3 months, respectively, Mann–Whitney U-test).

Apart from increased IOP, no complications related to subtenon TA injection were noted. In all cases, IOP had been well controlled using antiglaucoma drugs.

Discussion

In the current study, visual improvement peaked earlier in vitrectomized eyes than in nonvitrectomized eyes. This disparity in peaks corroborates previous pharmacokinetic results in rabbits.[10] On the other hand, visual improvement was not significantly different between the two groups.

TA is a long-acting synthetic corticosteroid that has approximately five times the anti-inflammatory potency of cortisol. Machemer *et al*.[11] used intravitreal TA to treat proliferative vitreoretinopathy for the first time in 1979; since then, it has been used widely to treat various ocular diseases, including DME. However, the Diabetic Retinopathy Clinical

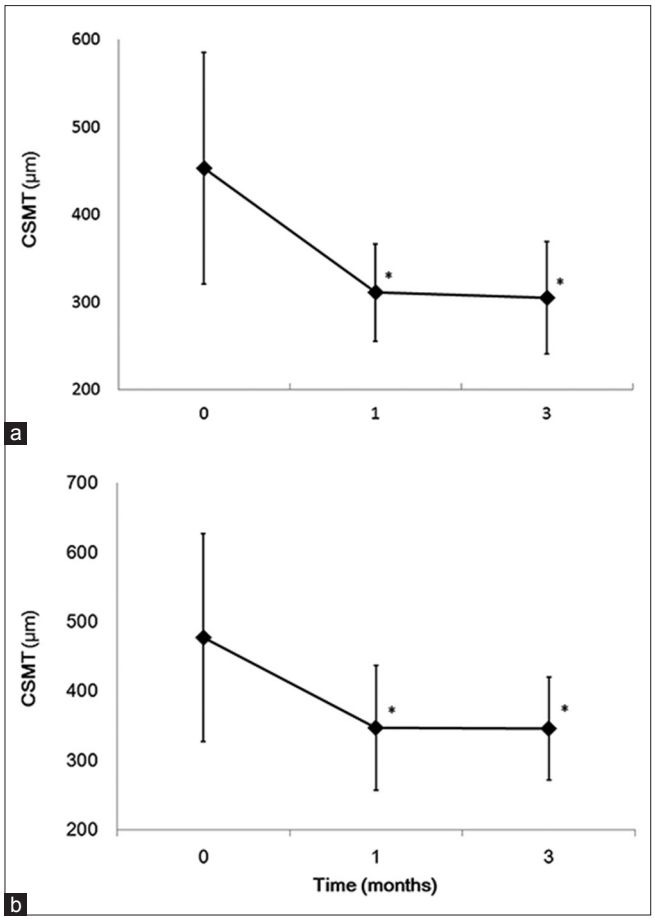

Figure 2: Change in central subfield macular thickness after subtenon triamcinolone acetonide injection to treat diabetic macular edema. (a) Vitrectomized group (b) nonvitrectomized group. The vertical lines indicate one standard deviation from the mean (*$P < 0.05$ compared to baseline)

Research Network (DRCR.net) reported that intravitreal TA had no long-term benefits for visual acuity in DME; indeed, poor visual outcome was mainly related to cataract change due to TA.[12] In contrast, although subtenon TA has not yet been established in a large study, it seems to have lower efficacy and higher safety than intravitreal injection has.[13,14]

Efficacy of subtenon triamcinolone acetonide in diabetic macular edema

Several studies have evaluated subtenon TA to treat DME. Bakri and Kaiser[15] and Tunc *et al*.[16] showed that subtenon TA could improve DME while Entezari *et al*.[17] and DRCR.net did not.[13] Entezari *et al*.[17] enrolled only advanced DME (mean visual acuity 20/160), and DRCR.net[13] included only mild DME (excluding those with 20/40 vision or worse). Thus, results of Entezari *et al*.[17] and DRCR.net did not represent its efficacy in universal DME. The current study also showed that subtenon TA could improve DME with accordance to Bakri and Kaiser[15] and Tunc *et al*.[16]

Comparisons of efficacy of subtenon triamcinolone acetonide between vitrectomized and nonvitrectomized

There were two small case series comparing the efficacy of subtenon TA between vitrectomized and nonvitrectomized eyes. Wada *et al*.[18] and Sato *et al*.[19] reported that anatomical outcomes of the vitrectomized were better than those of the nonvitrectomized. Because their studies[18,19] included small populations with incomparable baseline characteristics, further studies should be needed to confirm it. In the current study, more patients (sixty eyes) were enrolled with more comparable baseline characteristics [Table 1], and we did not find any significant difference between the groups in terms of outcomes – neither visual nor anatomical.

Pharmacokinetics of subtenon triamcinolone acetonide

Visual improvement peaked earlier in vitrectomized eyes than in nonvitrectomized eyes in this study. In a previous study, Park *et al*.[10] reported the intraocular pharmacokinetics of TA injected into the posterior subtenon space of rabbit eyes. Therein, intravitreal TA concentrations were higher in vitrectomized eyes than in nonvitrectomized eyes during the first 2 weeks; the half-life of TA in vitrectomized eyes was 23.3 days, which was shorter than its 28.9-day half-life in nonvitrectomized eyes. This implies that subtenon TA works sooner in vitrectomized eyes but lasts longer in nonvitrectomized eyes, which may be explained as follows: A fully formed vitreous inhibits the diffusion of TA into the vitreous cavity, and the TA concentration gradient therefore remains low in nonvitrectomized eyes. The current results corroborate the results of this study in rabbit eyes.

Limitations

Conversely, with regard to anatomical improvement, we found no disparity in peak efficacy between the groups. The depletion of efficacy, which is critical for revealing the pharmacokinetics, could not be analyzed in this study nor could the long-term efficacy of subtenon TA to treat DME. Because the majority of patients needed additional treatment (photocoagulation or anti-VEGF injection) 3 months after subtenon TA, it was impossible to analyze the results beyond this time. Although TA may have had a small impact on cataract development during those 3 months,[13] the lower rate of pseudophakia in nonvitrectomized eyes would have created bias. The effect of TA was evaluated in terms of anatomical and visual outcomes; however, the different visual acuity peaks did not correspond to CSMT differences. The pathogenesis of DME is rather complex and not fully understood. Other factors, such as VEGF,[20] or ILM status,[21] and previous PRP or lens status, could have had effects on the efficacy or pharmacokinetics of subtenon TA. With specific regard to baseline characteristics, there were significant differences in lens status and ILM. Although no studies have examined the pharmacokinetics of TA according to lens status, according to the pharmacokinetic studies of anti-VEGF agents, intraocular pharmacokinetics do not seem to be affected by lens status.[22,23] Similarly, there are no data on ILM status and intraocular pharmacokinetics. With the ciliary body known as the main route of drug clearance,[24] ILM status might not have much effect on pharmacokinetics. Nevertheless, the theory regarding a fully formed vitreous inhibiting the diffusion of TA into the vitreous cavity could not be proven in the current study.

Conclusions

Despite these limitations, the following conclusions can be drawn from the current study. Subtenon TA was an effective treatment for DME for 3 months both in vitrectomized

and nonvitrectomized eyes. It may be an alternative treatment option for DME, especially for patients with a low socioeconomic status. In contrast with previous results,[18,19] we did not find better outcomes in vitrectomized eyes than in nonvitrectomized eyes. In corroboration with an animal study, subtenon TA appears to improve vision faster in vitrectomized eyes although the improvements also decay more quickly. These results require confirmation in larger scale, randomized, controlled case series.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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