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Long-term clinical outcomes and therapeutic benefits of triamcinolone-assisted pars plana vitrectomy for proliferative vitreoretinopathy: A case study

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PURPOSE. *To investigate intraoperative visibility and long-term clinical outcome following triamcinolone acetonide (TA)–assisted pars plana vitrectomy (PPV) for proliferative vitreoretinopathy (PVR).*
METHODS. *A retrospective interventional noncomparative clinical study was carried out on 21 eyes from 21 patients with more than grade C2 PVR, all of whom underwent TA-assisted PPV. Two of the specimens were observed with an electron microscope. After treatment, outcome measures, including changes in best-corrected visual acuity (BCVA), intraocular pressure (IOP) elevation, corneal pathology, and occurrence of endophthalmitis, were recorded. Patient follow-up time was >36 months (mean ± standard deviation = 47.3 ± 6.7 months).*
RESULTS. *TA improved the intraoperative visualization of the epiretinal membrane (ERM), allowing it to be easily removed together with the partially internal limiting membrane (ILM) using microforceps. The excised tissue consisted of proliferative cells and an extracellular matrix underlying the ILM. After the operation, 71.4% of the eyes had improved BCVA. Three of the eyes showed sustained IOP elevation (14.3%); two of these cases were controlled by the administration of eyedrops, while the third required filtering surgery. In two cases, an absorption delay of the TA granule on the retinal surface was observed. One eye developed corneal stromal opacity. No other severe complications occurred during the observation period.*
CONCLUSIONS. *TA-assisted PPV offers improved visualization during the surgical management of PVR, and allows surgeons to excise the ERM safely and effectively without the risk of serious complications. (Eur J Ophthalmol 2007; 17: 392-8)*

KEY WORDS. *Triamcinolone acetonide, Vitrectomy, Long-term clinical outcomes, PVR*

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INTRODUCTION

During the morphogenesis of proliferative vitreoretinopathy (PVR), a fibrous membrane can form at the vitreoretinal interface. The contraction of this membrane can result in retinal detachment (RD) causing severe visual loss, and mild PVR occurs in approximately 5% of all RD cases.

Pars plana vitrectomy (PPV) is an established treatment for PVR that aims to remove as much of the residual vitreous or fibrous membrane as possible from the retina (1, 2). Although various surgical techniques, instruments, and adjuvants have been developed to assist with this procedure, the complete removal of the residual posterior hyaloid membranes can be difficult to achieve due to

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problems with visualization and toxicity. The development of indocyanine green (ICG) and trypan blue (TB) staining has greatly facilitated the peeling of the internal limiting membrane (ILM) and epiretinal membrane (ERM) in the treatment of various vitreoretinal diseases; as a result, this technique is now widely used by many surgeons (3-5). However, numerous clinical and experimental reports have recently suggested that intravitreal injections of ICG and TB can cause retinal damage (6-12).

We previously reported that triamcinolone acetonide (TA)–assisted PPV reduced the postoperative blood–ocular barrier breakdown with no apparent toxicity during the treatment of various intraocular diseases (13-16). In the present study, we investigated the long-term clinical outcomes and benefits of TA-assisted PPV for the treatment of PVR.

METHODS

Patients

A retrospective study was carried out on 21 eyes from 21 patients with more than grade C2 PVR and rhegmatogenous RD, all of whom underwent TA-assisted PPV at Kyushu University Hospital, Japan, between June 2001 and June 2003. The exclusion criteria were as follows: RD due to a highly myopic macular hole, penetrating eye trauma, uveitis, proliferative diabetic retinopathy, and patient age <18 years. Baseline PVR was characterized both preoperatively and intraoperatively according to the Retinal Society Classification (17).

The current study was carried out with approval from the relevant Institutional Review Board, and was performed in accordance with the Ethical Standards of the 1989 Declaration of Helsinki. The possible advantages and risks of the treatment were explained to all of the patients before surgery, and informed written consent was obtained from each patient.

Surgical procedures

Standard phacoemulsification was performed if required. A TA aqueous suspension (Kenakolt-A®; Bristol Pharmaceuticals KK, Tokyo, Japan) was prepared as described previously (13-16). After standard PPV was performed, 0.5 mL TA solution was injected with a 27-gauge needle into the midvitreous cavity and the vitreous base. Visible TA granules on the vitreous base were removed as thoroughly as possible by shaving with the cutter. Residual posterior hyaloid membrane and ERM-attached TA granules were removed using a silicone-tipped needle, surgical microforceps, and a diamond-dusted membrane scraper (DDMS; DORC, Phoenix, AZ).

Relaxing retinotomy and subretinal strand removal were performed. After correct retinal mobility was obtained, the retina was flattened with air or liquid perfluorocarbon, and endolaser photocoagulation was performed around the breaks and retinotomy edges. Silicone oil, C_3F_8, or SF_6 gas was injected into the intraocular lens (IOL) according to the patient's background or eye state. Small numbers of TA granules usually remained on the inferior retina. All of the patients received cataract surgery either preoperatively or intraoperatively for the purpose of the sufficient anterior vitrectomy. Postoperative glaucoma surgery (trabeculectomy) was required in one case. Three surgeons who had similar experience and technical expertise performed all of the operations (A.U., H.E., and Y.H.).

Transmission electron microscopy (TEM)

Two ERM specimens were analyzed by TEM. The membranes were fixed in 1% glutaraldehyde and 1% paraformaldehyde in PBS, postfixed in veronal acetate buffer osmium tetroxide (2%), dehydrated in ethanol and water, and embedded in Epon. Ultrathin sections were cut from blocks and mounted on copper grids. The specimens were observed with a JEM 100CX electron microscope (JEOL, Tokyo, Japan).

Clinical outcome

For each patient, the postoperative best-corrected visual acuity (BCVA), state of the retina, intraocular pressure (IOP) elevation, corneal pathology (persistent corneal erosion, ulcer, or corneal opacity), and occurrence of endophthalmitis were recorded by a physician without knowledge of the surgical history. A postoperative IOP >21 mmHg for >3 days was defined as showing sustained elevation. This was not considered to be a consequence of surgical invasion if it occurred >2 weeks postoperatively. Persistently elevated IOP was treated either with a β-blocker (Timoptol® 0.5%; Santen Pharmaceutical Co., Ltd., Osaka, Japan) and latanoprost (Xalatan®; Pfizer Japan Inc., Tokyo, Japan) or by surgery.

RESULTS

The patients' details are shown in Table I. The mean age ± standard deviation (SD) was 60.0±13.5 years, with a range of 20–81 years. The mean follow-up period ± SD was 47.3±6.7 months.

After injection of the TA suspension, and suction removal of excess TA granules, the posterior hyaloid membranes and ERM were observed as white islands on the retinal surface. These membranes were removed using a silicone-tipped needle, DDMS, or surgical ILM forceps (Fig. 1, A–D). If required, TA injection was performed several times during the operation. At the end of the surgery, a small amount of TA granules were usually left (up to 1 mg)

TABLE I - CHARACTERISTICS AND MAIN OUTCOME OF THE PATIENTS

Case	Age/ Sex	Classi-fication of PVR	Previous surgical procedure (Original disease)	Preop. BCVA	Postop. BCVA	Final status of retina	Additional surgeries	Complications
1	81/M	C2	1X VIT (r-RD)	20/200	20/200	Attached	-	IOP elevation (sustained postoperative)
2	44/M	C2	1X SB (r-RD)	20/600	20/200	Attached	-	IOP elevation (early postoperative)
3	49/M	D1	None (r-RD)	LP	HM	Attached	SO removal	Delay of absorption of TA granule
4	66/F	D1	None (r-RD)	HM	HM	Attached	SO removal	
5	54/M	C2	1X SB, 1X VIT (r-RD)	HM	20/640	Attached	-	IOP elevation (early postoperative)
6	50/M	C3	1X VIT (r-RD)	CF	20/100	Attached	-	
7	40/F	D1	None (r-RD)	LP	20/800	Attached	SO removal	IOP elevation (sustained postoperative)
8	60/M	C2	2X VIT (r-RD)	20/400	20/800	Attached	-	
9	57/M	D2	1X VIT (r-RD)	LP	LP	Not attached under SO	2X VIT	Recurrent detachment, Ocular hypotension, Corneal opacity
10	60/M	C3	1X SB, 1X VIT (r-RD)	HM	20/320	Attached	-	
11	49/F	C2	1X VIT (r-RD)	20/800	20/100	Attached	Trabeculectomy	IOP elevation (sustained postoperative)
12	62/M	C3	1X VIT (r-RD)	HM	20/600	Attached	1X VIT (membrane peeling) +SO removal	Recurrent detachment
13	55/F	C2	None (r-RD)	20/400	20/40	Attached	1X VIT (relaxing retinotomy)	Recurrent detachment
14	42/F	C2	None (r-RD)	HM	20/100	Attached	-	
15	64/M	C2	None (r-RD)	CF	HM	Attached under SO	-	Delay of absorption of TA granule
16	20/M	C2	1X SB (r-RD)	20/320	20/50	Attached	-	IOP elevation (early postoperative)
17	61/F	C2	1X VIT (r-RD)	HM	CF	Attached	-	
18	68/F	D1	None (r-RD)	CF	CF	Attached	SO removal	
19	77/F	C3	None (r-RD)	LP	20/400	Attached	-	
20	71/M	C2	1X SB (r-RD)	20/500	20/200	Attached	-	
21	45/M	C3	None (r-RD)	HM	20/40	Attached	-	IOP elevation (early postoperative)

r-RD = Rhegmatogenous retinal detachment; VIT = Vitrectomy; SB = Scleral buckling; Preop. = Preoperative; Postop. = Postoperative; BCVA = Best corrected visual acuity; LP = Light perception; HM = Hand movement; CF = Counting fingers; SO = Silicone oil; IOP = Intraocular pressure; TA = Triamcinolone acetonide

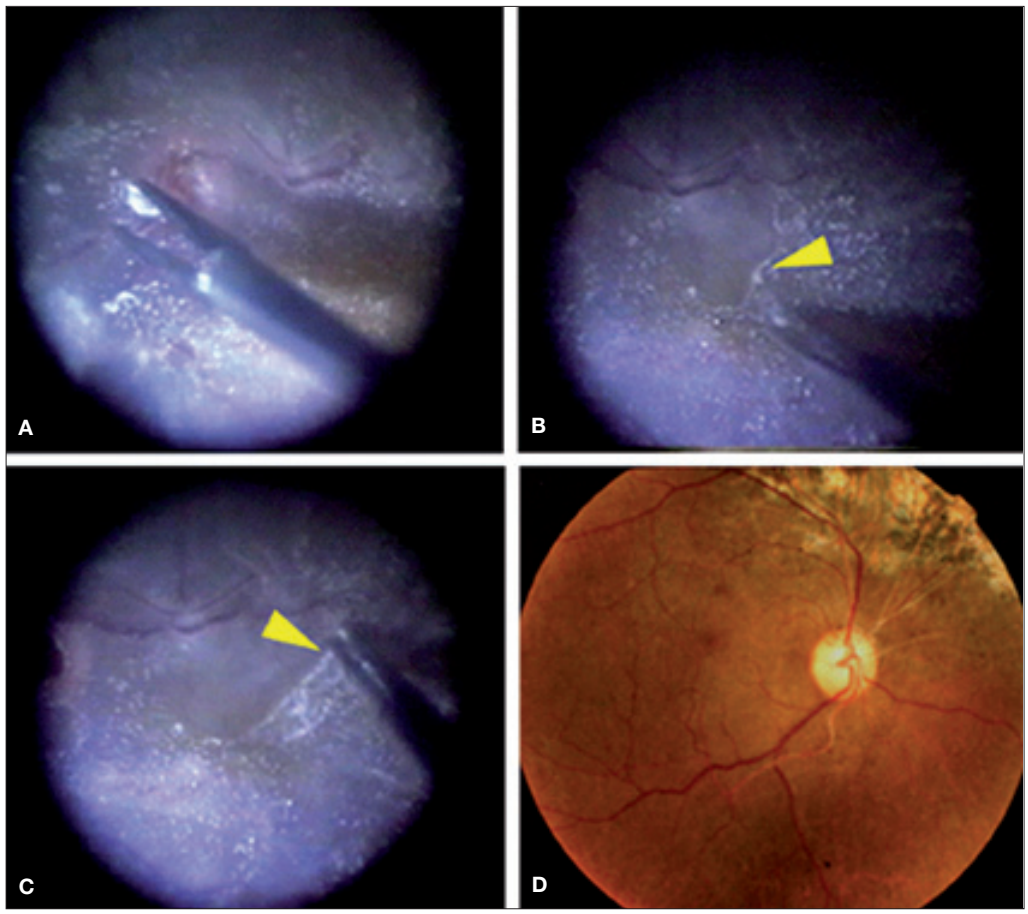

Fig. 1 - *Intraoperative and postoperative findings for an eye with proliferative vitreoretinopathy.* **(A)** *After the injection of a triamcinolone acetonide (TA) suspension, TA granules that adhered to the thin posterior hyaloid and the fibrous preretinal membrane (especially premature membranes) were observed as white islands on the retinal surface.* **(B, C)** *The membranes were removed with surgical internal limiting membrane forceps (arrowheads).* **(D)** *The retina became completely attached 3 weeks after surgery.*

on the inferior retina. Retinotomies or retinectomies were performed in 4 of 21 eyes including reoperation. Silicone oil was injected into a total of 6 eyes among 21 eyes in the primary PVR operation. In other cases, we injected gas (SF_6 or C_3F_8) as tamponade agent. Two excised membranes with TA granules were examined using TEM (Fig. 2A), and were found to consist of ERM and layers of ILM that were completely detached from the retinal surface. The retinal side of the ILM was rough with evidence of Müller cell debris, while various migrated cells (including glial cells, retinal pigment epithelial cells, and myofibroblasts) were attached to the vitreous side. These cells were intermingled with a dense collagen extracellular matrix of both vitreous hyaloid and newly synthesized collagen fibers (Fig. 2B).

Anatomic success, which was defined as complete retinal reattachment after silicone oil removal, was finally achieved in 19 of the 21 eyes (90.5%). In one of the remaining two cases RD remained at the lower two quadrants, while the second case underwent reattachment using silicone oil. The silicone oil was not removed in either of these cases. After primary PVR operation, 14.3% (3 of the 21 cases) was the rate of retinal redetachment (Tab. I; Cases 9, 12, and 13). In 8 of 21 eyes (38.1%), additional operation was required including silicone oil removal, trabeculectomy, and vitrectomy by the time of the last observation, and the average number of operations was 1.4.

The postoperative BCVAs ranged from light perception to 20/40. Eleven patients (52.3%) had a VA >20/400. The BCVA improved in 15 of the eyes (71.4%), decreased in 2 eyes (9.5%), and remained unchanged in 4 eyes (19.0%). At the end of the follow-up period, 19 of the patients were pseudophakic and 2 were aphakic. In 7 of the 21 eyes (33.3%), the IOP was elevated to >21 mmHg in the early postoperative period. The IOP normalized within 1 week in 4 of these eyes, while a high IOP persisted in the remaining 3 eyes (14.3%). Two of these cases were treated with a β-blocker and latanoprost, while the third required glaucoma surgery.

The TA granules that remained on the retinal surface disappeared <2 weeks after the operation in almost all cases. Delayed TA absorption was observed in two cases, but the granules disappeared within 1 month postopera-

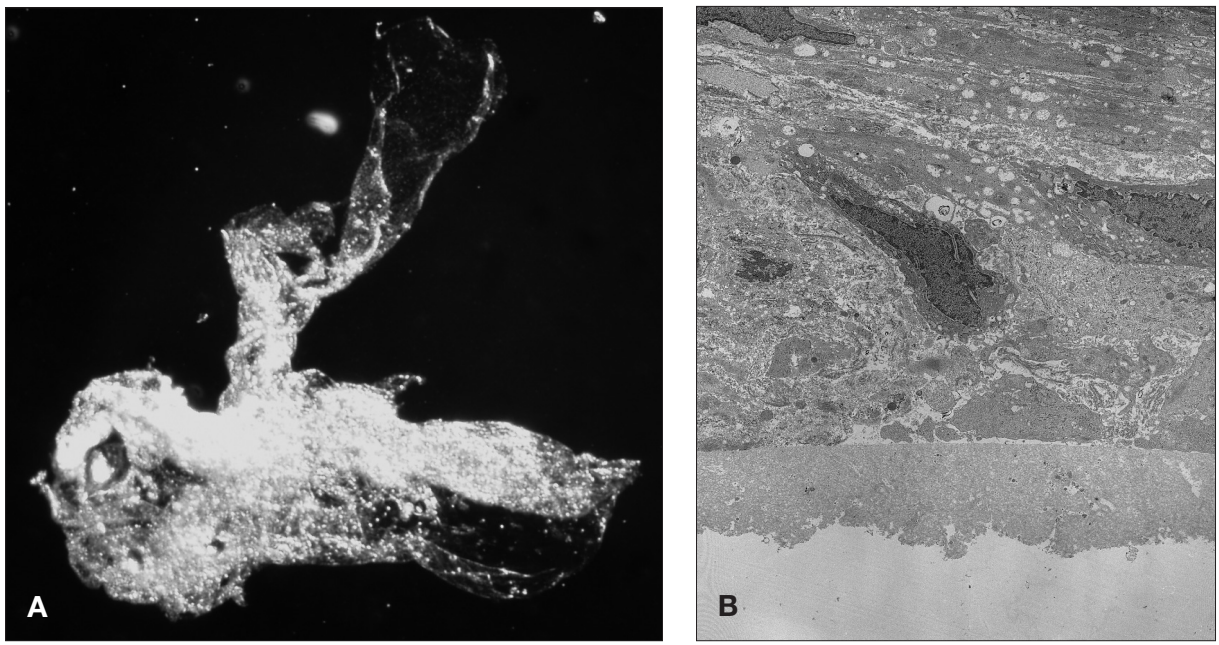

Fig. 2 - *Histologic analysis of epiretinal membranes (ERMs) with transmission electron microscopy.* **(A)** *After removal of ERMs with triamcinolone acetonide granules.* **(B)** *All layers of excised internal limiting membrane (ILM) tissue were totally detached from the retinal surface. The retinal side of the ILM was rough with Müller cell debris, while migrated cells (such as glial cells, RPE cells, and myofibroblasts) were attached to the vitreous side. These cells were intermingled with a dense collagen extracellular matrix of vitreous hyaloid and newly synthesized collagen fibers.*

tively. One eye developed corneal stromal opacity. There were no other severe adverse complications (such as persistent corneal ulcer, postoperative severe inflammation, or endophthalmitis).

DISCUSSION

In PVR surgery, complete removal of the ERM and a reduction in postoperative inflammation might be a logical strategy to prevent redetachment (18); however, this can be difficult to achieve despite the development of specific surgical techniques and instruments.

In the current study, we demonstrated that TA improved the visibility of ERM, allowing their easy, safe, and thorough removal during surgery without the need for ICG and TB staining, which are associated with retinal damage (6-12). TA also facilitated excision of the ILM, and greatly improved the visibility of the obscure anterior vitreous and vitreous base. We were therefore able to remove a larger amount of residual vitreous gel than during a PPV without the use of TA. The patient outcome in the present study was generally good, with 52.3% of patients reporting a VA >20/400. The BCVA improved in 71.4% of the patients, and retinal reattachment was achieved in 90.5% of the cases. This compared favorably with recent reports on the management of PVR (19-21).

TA is a water-insoluble steroid that inhibits various postoperative inflammatory reactions, and TA granules have been shown to be safe for administration to the retina (14, 22). Previous studies have reported good results following vitrectomy using TA for refractory uveitis (15), while animal work has revealed an inhibitory effect of TA on PVR (23, 24). We therefore speculate that, in the present study, the intraocular use of TA decreased postoperative inflammation, and inhibited subsequent fibrous tissue formation and the recurrence of RD to some extent. This possibility is supported by clinical observations (13, 16, 25), and by the finding that TA inhibits RPE and retinal glial cell proliferation in vitro (26).

Corticosteroids are known to elevate IOP in susceptible patients, much like the elevation of IOP observed in some eyes following TA injection (27-30). In cases where TA is used as an adjuvant, our experience suggests that such elevation of postoperative IOP is considered satisfactory (13-16). In the present study, increased postoperative IOP occurred in 3 out of 21 cases (14.3%); among these, antiglaucoma eyedrops controlled the elevation in two cases,

while the third required surgery. Nevertheless, the elevated IOP caused by TA remains an important problem that must be addressed in the future. Cataract formation is another serious complication of intraocular steroid treatment, which has also been associated with TA injection (31-33). However, we could not ascertain the effect of TA-assisted PPV on the development of cataracts in the present study, as no phakic eyes were enrolled.

Previous reports have shown that TA and silicone oil are safe for use in the retina (34). In the present study, however, we observed two cases of delayed TA granule absorption on the retinal surface for >6 months, even though the half life of intravitreous TA has been reported as 1.6 days in vitrectomized eyes (35, 36). In these two cases, we speculate that hyposecretion of the aqueous humor occurred due to ciliary body dysfunction following contact with silicone oil. In the remaining 19 cases, residual TA granules were reabsorbed within 2 weeks. We therefore suggest that caution should be exercised when combining the use of TA and silicone oil. Endophthalmitis is another important risk associated with the use of TA. In the present study, we did not observe any postoperative infection, and our previous investigations have shown the incidence of endophthalmitis after TA-assisted PPV to be 0.053% (37).

We previously applied TA-assisted PPV to various intraocular diseases and obtained good results (13-16). The method has also been shown to improve the results of PVR surgery in the short term (24) and has potential use for obtaining improved PVR treatment results in the long term. Future randomized studies should be conducted to determine whether TA-assisted PPV offers visual benefits, and consequent improved surgical outcomes, before it can be established as an effective and safe method for PVR surgery.

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