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Research paper

A novel design of one-side coated biodegradable intrascleral implant for the sustained release of triamcinolone acetonide

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Abstract

The purpose of this study was to evaluate the efficacy and safety of biodegradable intrascleral implants for the slow release of triamcinolone acetonide (TA). Intrascleral implant (1 mm thick; 3 mm diameter) was made of PLA (poly(D,L-lactide)) containing 6.4 mg of TA with one-side coating of high molecular weight PLA to render unidirectional drug absorption through the sclera. *In vitro* TA release was evaluated by liquid chromatography–mass spectroscopy for 90 days. *In vivo* release of TA was measured in aqueous humor, vitreous, and retina–choroid at 1, 2, 4, 8, and 12 weeks after intrascleral implantation in 20 rabbit eyes. Implant toxicity and biocompatibility were evaluated by slit lamp examinations, indirect ophthalmoscopy, intraocular pressure measurements, electroretinography, and histological examinations. *In vitro* studies demonstrated that the implants released TA in a controlled manner over 90 days. *In vivo*, TA was detected in aqueous humor until 4 weeks and in retina–choroid until 8 weeks after implantation, but was detected constantly over 12 weeks in vitreous. No significant retinal toxicity was observed. These results suggest that the devised intrascleral implant offers a promising controlled release system for the delivery of TA to the posterior segment of the eye.

Keywords: Triamcinolone acetonide; Poly(D,L-lactide) (PLA); Intrascleral implant; One-side coating

1. Introduction

Synthetic corticosteroids, especially triamcinolone acetonide (TA), have been used to treat inflammatory and proliferative ocular disorders, such as uveitis [1,2], cystoid macular edema [3–5], proliferative vitreoretinopathy [6], and choroidal neovascular membrane secondary to age related macular degeneration [7,8]. The systemic administration of corticosteroid is the most common method to deliver drugs to the posterior eye, but may be problematic to require large doses and produce side effects. Topical instillation does not yield therapeutic drug levels to the posterior eye due to lacrimation, tear drainage, and the length of the diffusion path [9–11].

Intravitreal injections provide the most direct approach to the posterior segment of the eye, but their use is associated with potential side effects, such as retinal detachment, vitreous hemorrhage, endophthalmitis, cataract, and glaucoma [12]. Moreover, repeated injections are required to maintain therapeutic drug levels, and these are often poorly tolerated by patients.

Transscleral delivery provides another route of drug delivery to the posterior segment of the eye. The average surface area of the human sclera (17 cm^2) accounts for 95% of the total surface area of the globe and provides a significantly larger avenue for drug diffusion to the eye interior than the 1 cm^2 surface area of the cornea [13]. Moreover, in addition to its large surface area and high degree

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of hydration, the sclera is permeable to a wide range of solute molecular weights [14].

It has been reported that scleral permeability is comparable to that of the corneal stroma and that solute lipophilicity does not seem to affect scleral permeability markedly [15]. Moreover, the rabbit sclera is permeable to solutes ranging in molecular weight up to 150 kDa, but permeability declines exponentially with increasing molecular weight and molecular radius [16]. Mora et al. [17] reported that the human sclera is permeable to TA and found that the human scleral permeability coefficient (Ps ± SEM) for TA is $1.47 \pm 0.17 \times 10^{-5}$ cm/s. TA has a relatively small molecular weight (434.5 Da) and high lipophilicity, and thus, it can easily penetrate the sclera.

It is also important to consider that transscleral drug delivery is governed, in part, by the transient diffusion of a solute across the sclera, which typically occurs over a time course of minutes. Furthermore, extensive systemic absorption occurs during transscleral delivery, and thus, it may be difficult to achieve adequate drug levels without incurring unwanted side effects, unless some type of sustained-release formulation or device is used. In addition, it is difficult to achieve constant drug levels without supratherapeutic drug peaks or subtherapeutic drug troughs.

The utilization of some type of sustained-release delivery system would thus appear to be necessary for the successful utilization of transscleral drug delivery. An ideal sustained-release transscleral drug delivery system would provide controlled, long-term drug release, specific scleral site delivery, and prolonged drug-sclera contact time. Such a system would permit improved drug flux through thinner regions of the tissue, potentially allow treatment to specific posterior segment of the eye, and minimize systemic drug absorption by the conjunctival vasculature and lymphatics [18].

In this study, a novel designed implant for sustained release of triamcinolone acetonide was developed for effective transscleral delivery. The implant was designed as a form of disc (3 mm diameter, 1 mm thickness) by using poly(D,L-lactide) (PLA) with molecular weight (MW) of 125,000 and coated with higher molecular weight PLA (MW 300,000) on the one side to prevent extensive systemic absorption through conjunctival blood vessels and lymphatics. To determine the efficacy of this TA implant, the *in vitro* and in *vivo* release profiles of TA were investigated, and its toxicity and biocompatibility were evaluated in rabbit eyes.

2. Materials and methods

2.1. Preparation of TA implant

TA implants were prepared by dissolving 20 mg of PLA (MW 125,000, Polyscience, Inc., USA) and 80 mg of powdered crystalline TA (Dongkwang Pharmacy, Co., Korea) in 10 ml of dichloromethane. Distilled water (2 ml) was then added to form an emulsion, which was then frozen at −80 °C, and lyophilized for 24 h to obtain a homogenous cake. Eight milligrams of cake (containing 6.4 mg of TA) was then placed in a stainless steel mold and compressed in a hot template (130 °C, 1 h, 1 MPa) and a disc (1 mm thick and 3 mm in diameter) shaped implant was thus obtained. To make one-side coated TA implant, high molecular weight PLA (MW 300,000, Polyscience, Inc., USA) was dissolved in 20% dichloromethane and placed onto a glass slide to make film with 20 μm thickness. After drying in a hood for 24 h, this film was peeled off and draped over the stainless steel mold. TA implant was then placed on the film to cover one side of the disc and compressed in the template (120 °C, 1 h, 1 MPa). The TA implants were then sterilized before using with gamma radiation (twice at 1390 rad/min for 600 s). Fig. 1 shows the TA implant.

2.2. Observation of implant surfaces

TA implant degradation was observed by scanning electron microscopy (S-570, Hitachi, Japan) by comparing implant surfaces before and 8 and 12 weeks after intrascleral implantation, by coating implants with gold and observing them at magnifications of 40, 500, and 10,000×.

2.3. In vitro release study

A TA implant was placed in 10 ml of phosphate buffered saline (PBS, pH 7.4) in a closed vial and then immersed in a shaking water bath at 37 °C. At indicated intervals, the entire volume was sampled and 10 ml of fresh PBS was added to the sample vial. Collected samples were centrifuged at 3000 rpm for 5 min, filtered using a 0.2 μm syringe filter, and stored at 4 °C. The total amount of TA in medium was measured by high performance liquid chromatography (HPLC, LC-10A, Shimadzu Inc., Japan) using a C-18 reversed-phase column (Capcell Pak C18 UG120, 250 × 4.6 mm; Shisheido Fine Chemicals, Japan) equipped with a 252 nm detector. The flow rate was 1.0 ml/min and the mobile phase was 45% acetonitrile and 55% of water by

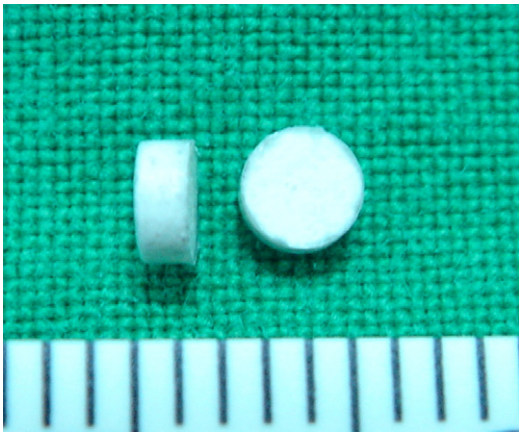

Fig. 1. The devised biodegradable one-side coated triamcinolone acetonide intrascleral implant (thickness 1 mm; and diameter 3 mm).

volume. The injection volume was 100 μl and the running time was 15 min.

2.4. Intrascleral implantation

Animal experiments were reviewed and approved by the Animal Care Committee at the Kyungpook National University and followed National Institutes of Health guidelines for the care and use of laboratory animals (National Institutes of Health publication no. 85-23, rev. 1985). Twenty eyes of 20 New Zealand white rabbits, weighing 2.0–2.5 kg were used to study *in vivo* TA release. Briefly the procedure used was as follows. A rabbit was anesthetized with an intramuscular injection of xylazine hydrochloride (2 mg/kg) and ketamine hydrochloride (5 mg/kg). Proparacaine 1% was instilled topically onto the eye. After exposing the sclera, a half thickness scleral pocket was made using a crescent knife 3 mm from the limbus. A TA implant was then inserted into the scleral pocket with the coated side facing toward the conjunctiva and the scleral wound was sutured with 8–0 nylon and conjunctiva with 8–0 vicryl. Animals were euthanized with an overdose of intravenous pentobarbital sodium at 1, 2, 4, 8, and 12 weeks after implantation and eyes were immediately enucleated. After removal of TA implants for scanning electron microscopic analysis, enucleated eyes were frozen at −80 °C, and aqueous humor, vitreous and retina/choroid were removed from frozen eyes using a razor.

2.5. In vivo release study

The concentrations of TA in ocular tissues (aqueous humor, vitreous, retina/choroid) were measured by HPLC. TA was extracted from tissue by adding 3 ml of 0.2 M HCl to tissue samples. Mixtures were homogenized and centrifuged at 3000 rpm for 5–min, and supernatants were then collected, frozen rapidly in liquid nitrogen, and dried in a lyophilizer. Lyophilized supernatants were then dissolved in 1 ml of acetonitrile, filtered through a 0.2 μm syringe filter, and stored at 4 °C for HPLC analysis. The other HPLC procedures used were same as those described above for the *in vitro* study.

2.6. Implant toxicity and biocompatibility

2.6.1. Clinical observations

Slit lamp examinations, measurements of intraocular pressure (Tonopen XL, Mentor Co., USA), and indirect ophthalmoscopy were performed before and at 1, 2, 4, 8,

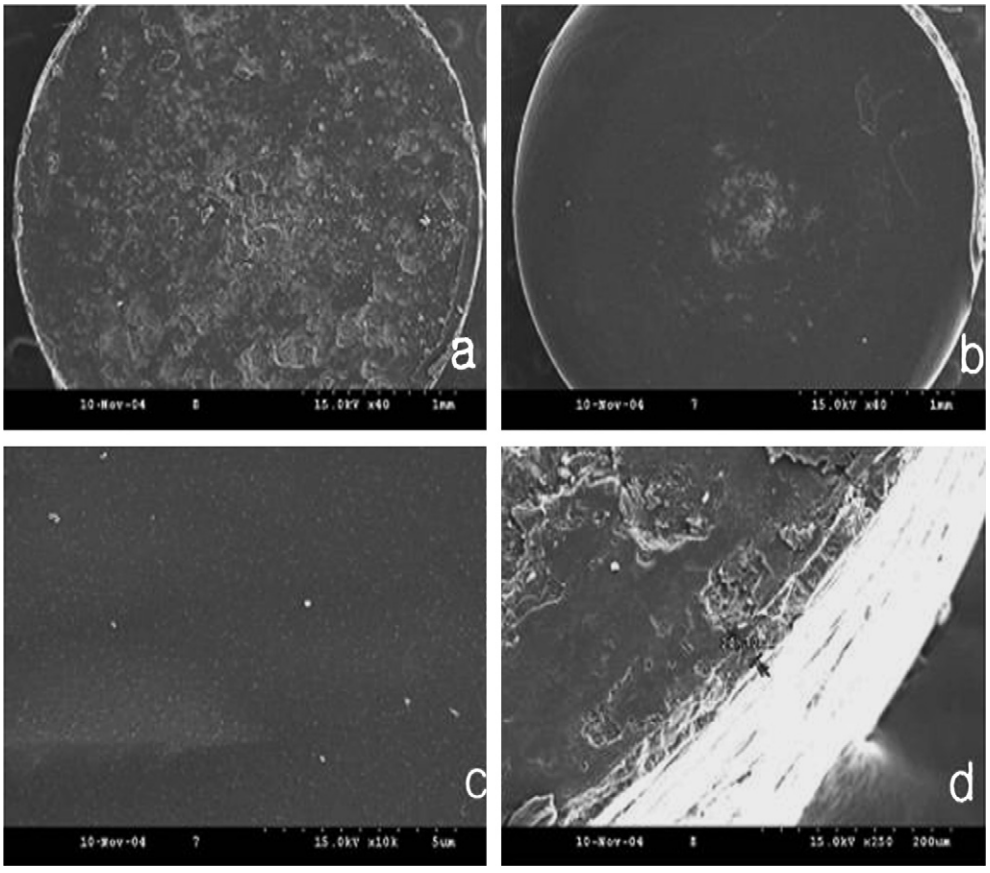

Fig. 2. Scanning electron microscopic photographs of the triamcinolone-loaded PLA implant before intrascleral implantation: (a) scleral side (40×), (b) conjunctival side, which has a high MW PLA coating (40×), (c) conjunctival side (10,000×), (d) high MW PLA side coating (500×).

and 12 weeks after intrascleral implantation to evaluate biocompatibility and possible toxicity.

2.6.2. Electrophysiological and histological studies

After pupil dilatation with 1% tropicamide and 2.5% phenylephrine, rabbits were dark adapted for 30 min. The scotopic electroretinograms (UTAS E-2000, LKC Technology, USA) were recorded before and 1, 2, 4, 8, and 12 weeks after implantation. Changes in scotopic b-wave amplitudes before and after intrascleral implantation were analyzed using the paired Student's *t*-test. Results were considered statistically significant for p values of <0.05.

At each time point, one eye was enucleated for histological examination. Eyes were immersed in a mixture of 4% glutaraldehyde and 2.5% neutral buffered formalin for 24 h. Eye specimens were then embedded in paraffin, sectioned with a microtome, and stained with hematoxylin and eosin.

3. Results and discussion

3.1. Observation of TA implant surfaces

The surfaces of retrieved implants were evaluated by scanning electron microscopy. Coated side (conjunctival side) of the implant had smooth surfaces due to the high MW PLA film (Fig. 2b and c), whereas opposite side (scleral side) were rougher (Fig. 2a). Lateral side (Fig. 2d) was shown to be coated with high molecular weight PLA and thickness of coating film is approximately 20 μm. Eight weeks after implantation, some pores were noted in scleral side (Fig. 3a and b), but the coated lateral (Fig. 3c) and conjunctival (Fig. 3d) sides were well preserved, though some surface cracking was observed. At 12 weeks, scleral sides were more eroded (Fig. 4a and b), whereas lateral (Fig. 4c) and conjunctival (Fig. 4d) sides showed some cracks in the high MW PLA coating.

When TA is administered by subconjunctival or subtenon injection, the main barriers to transscleral drug delivery are the sclera, choroidal vasculature, and clearance through the conjunctival lymphatics/blood vessels [18]. Robinson et al. [19] evaluated vitreous drug levels following a sub-Tenon's injection of triamcinolone acetonide in rabbits, and selectively eliminated the influence of conjunctival lymphatic/blood vessels with an incised 'conjunctival window'. They suggested that conjunctival lymphatics/blood vessels are an important barrier to the transscleral delivery of triamcinolone acetonide. Experiments were also performed to compare the delivery of sodium fluorescein to the retina by periocular injection and by using a unidirectional episcleral exoplant [20]. The exoplant allowed release of sodium fluorescein on the episcleral side but not on the

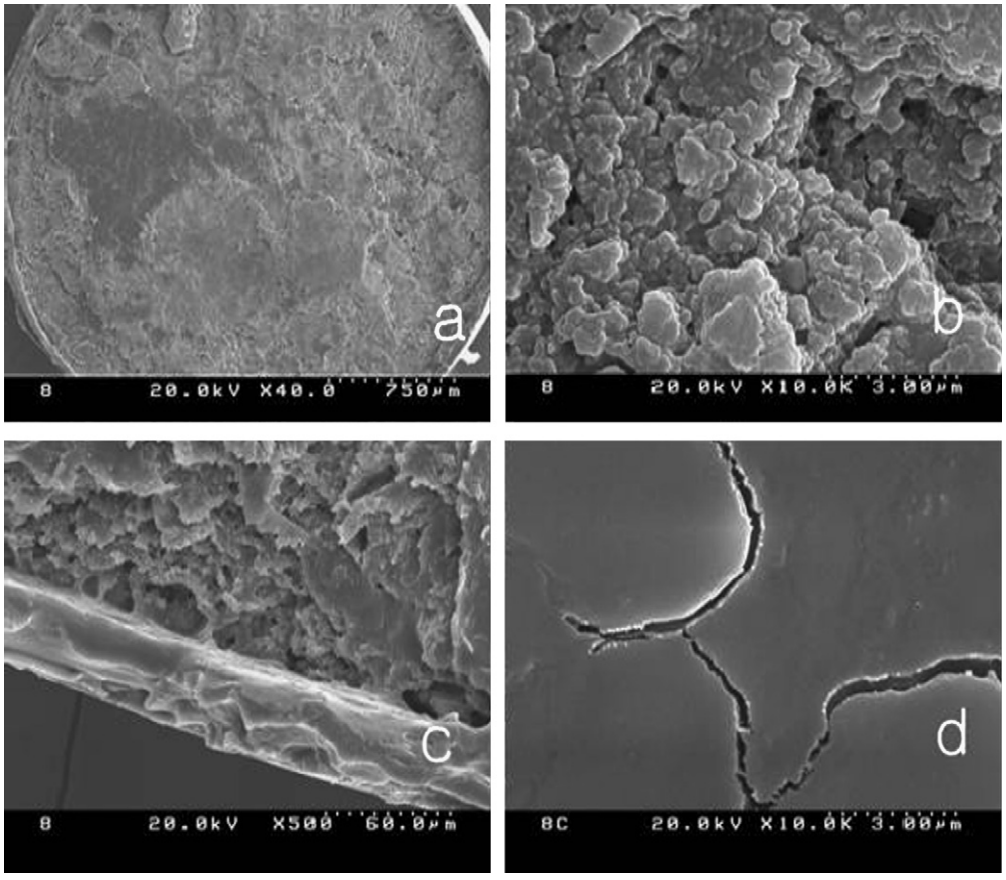

Fig. 3. Scanning electron microscopic photographs of a triamcinolone-loaded PLA implant 8 weeks after intrascleral implantation: (a) scleral side (40×), (b) scleral side (10,000×), (c) side coating (500×), (d) conjunctival side (10,000×).

conjunctival side. Furthermore, higher levels of sodium fluorescein were detected in the retina after delivery using a unidirectional episcleral exoplant than after periocular injection. The results of these studies suggest that conjunctival/episcleral clearance mechanisms play a significant role in reducing intraocular drug penetration. In the present study, we used one-side coated TA implant with an outer biodegradable high MW PLA barrier to prevent drug absorption through conjunctival blood vessels and lymphatics. Although we did not examine TA blood levels in rabbits after intrascleral implantation to determine systemic TA absorption levels, the high MW PLA coated surface remained intact at 3 months post implantation by scanning electron microscopy. Thus, the high MW film prevented direct contact between TA and conjunctival blood vessels and lymphatics, and thus, minimized systemic absorption and facilitated unidirectional drug absorption through the sclera.

3.2. In vitro release of TA from implants

Cumulative TA release from TA implants showed a biphasic profile with an initial burst of TA at 24 h followed diffusional release (Fig. 5). Over the first 24 h, the amount of TA released was 66.5 ± 27.4 μg (approximately 1.4% of the TA loading). Subsequently, TA was released at 4.7 ± 3.1 μg per day and 8% (539 μg of 6.4 mg) was released over 90 days *in vitro*, which means that the implant can release TA over substantially longer than 90 days.

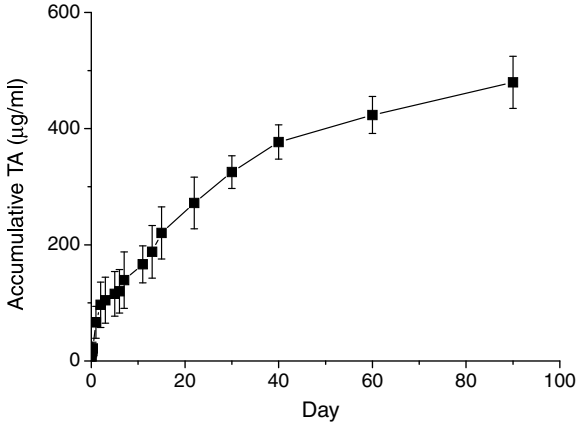

Fig. 5. *In vitro* release profiles of TA from the implant.

This biphasic release pattern *in vitro*, resembles those of similar biodegradable implants [21,22]. According to Kimura and Ogura [23], biodegradable implants made of PLA or PLGA showed distinct release profiles. The initial burst observed within 24 h may be due to the rapid release of the drug deposited on the implant surface and to water channels in the matrix. However, during the second stage, the drug is released slowly in a controlled manner as determined by the rate of degradation of the polymer. In our

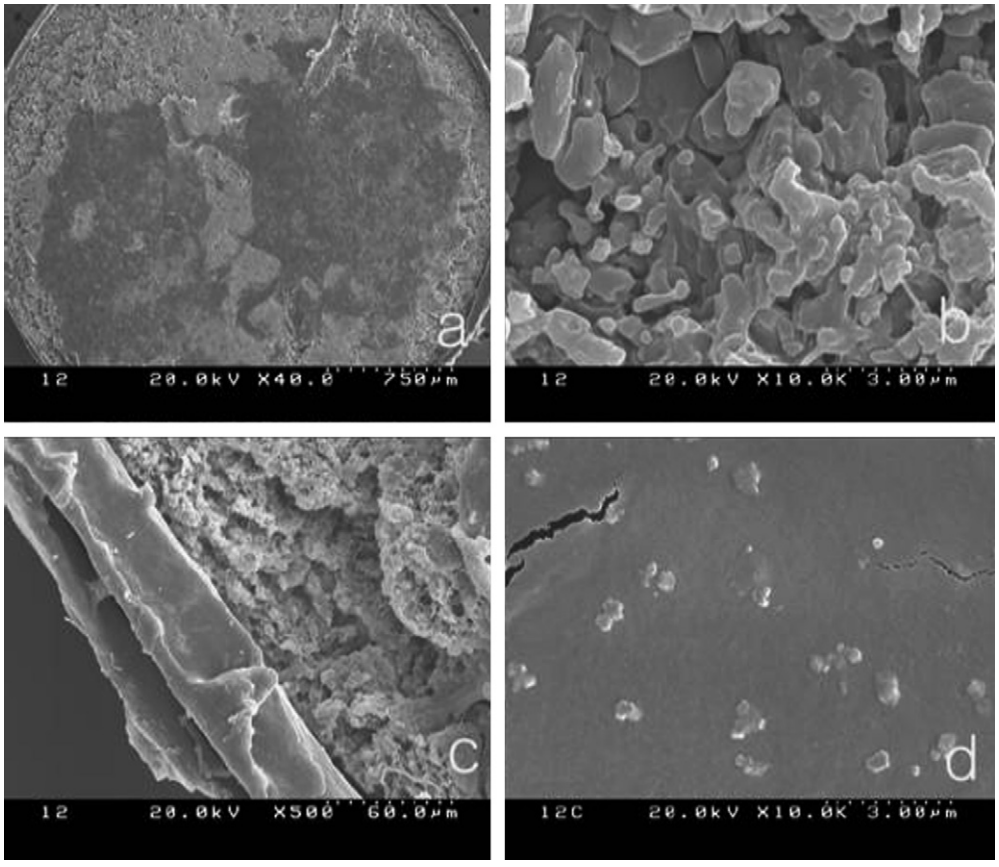

Fig. 4. Scanning electron microscopic photographs of a triamcinolone-loaded PLA implant 12 weeks after intrascleral implantation: (a) scleral side (×40), (b) scleral side (×10,000), (c) side coating (×500), (d) conjunctival side (×10,000).

study, the TA implant showed rapid drug release during first 24 h and then a constant release profile over 90 days *in vitro*. However, this rate of TA release can be controlled by changing the TA loading and the molecular weight of the PLA polymer.

3.3. In vivo release of TA from implants

The accumulative and mean concentrations of TA in aqueous humor, vitreous and retina/choroids at various times after implantation are plotted in Figs. 6 and 7, respectively. TA had proportionally released until 4 weeks after implantation in aqueous humor and retina/choroid (Fig. 6). However, TA was not detected in aqueous humor at 8 weeks and in retina/choroid at 12 weeks after implantation. But in the vitreous, TA levels remained constant through the initial 12 weeks (Fig. 7).

It is unclear why TA detected in vitreous is more longer than in aqueous or retina/choroid. We measured TA levels in ocular tissues for 3 months. But in other studies of intrascleral betamethasone implants [21,24], intraocular drug concentrations were measured over 1 or 2 months post-implantation, respectively. Possible mechanisms of these findings are drug clearance via choroidal blood vessels and counterdirectional fluid currents due to uveoscleral flow or hydrostatic/osmotic pressure differences, all of which result in bulk flow from the vitreous to the choroid and episcleral regions [18].

It was interesting to find that maximum TA concentrations in tissues were detected 2 weeks post-implantation in the present study, as another study on a betamethasone intrascleral implant also produced a maximum intraocular concentration at 2 weeks post-implantation [21,24]. It has been suggested that a certain time is required for drugs to traverse the sclera and choroid-RPE barrier to reach the vitreous cavity [17,25].

Several reports have been issued on the pharmacokinetics of intravitreal TA (IVTA) administration. Scholes et al [26] reported that mean vitreal TA levels after a 0.4 mg IVTA injection in rabbit eyes were 235 ± 85 μg immediately after injection, 90 ± 50 μg at 3 days, and 66 ± 19 μg at 13 days, but that no TA was detected in five of six eyes at 21 days post-injection. Mason et al [27] reported that intravitreal TA concentrations in human eyes after a 4 mg of intravitreal TA injection were 48–380 ng/ml at 1.25–2.75 months. Chin et al. [28] reported that TA was detected in only 1 eye (0.22 μg/ml) in a vitrectomized rabbit group as compared with 4 of 6 eyes (0.92 ± 1.25 μg/ml) in a non-vitrectomized rabbit group at 30 days after a 0.3 mg intravitreal TA injection. Beer et al. [29] demonstrated that the half-life of 4 mg IVTA by assaying from the anterior chamber in non-vitrectomized human eyes was 18.7 ± 5.7 days, whereas for vitrectomized eyes it was 3.2 days, and that complete drug elimination was achieved at 93 ± 28 days. In clinical practice, retreatment intervals are approximately 3 months, but no standard dosage schedule for re-injection has been established [1–5,7,8]. In the present study, intravitreal TA concentrations were 347–857 ng/ml at 1–12 weeks, and intravitreal TA levels were constantly maintained throughout 12 weeks. However, the optimal intravitreal TA level required to suppress inflammation and inhibit the breakdown of the blood retinal barrier has not been determined.

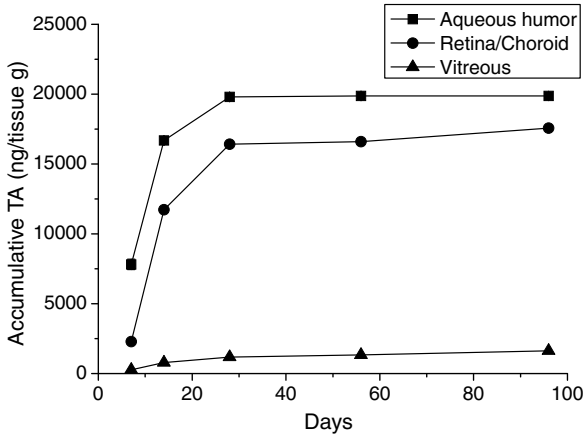

Fig. 6. Accumulative concentration of triamcinolone acetonide in aqueous humor, vitreous, and retina/choroid after intrascleral implantation.

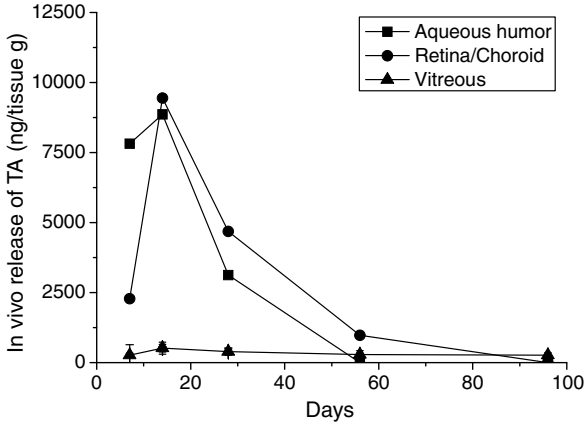

Fig. 7. Concentration of TA in aqueous humor, vitreous and retina/choroid after intrascleral implantation.

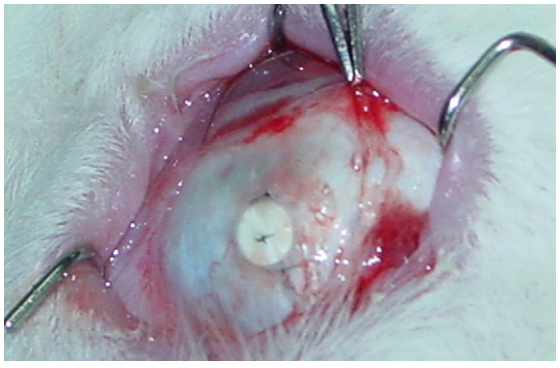

Fig. 8. Photograph of implantation site 1 week after the intrascleral implantation of the TA-loaded PLA implant.

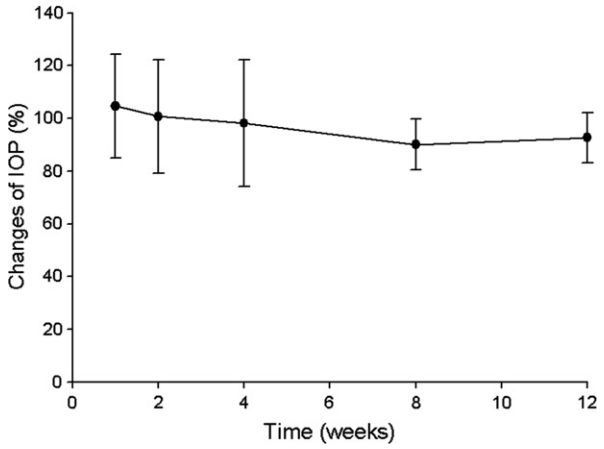

Fig. 9. Changes in intraocular pressure after intrascleral implantation. $p > 0.05$ by paired Student's t-test.

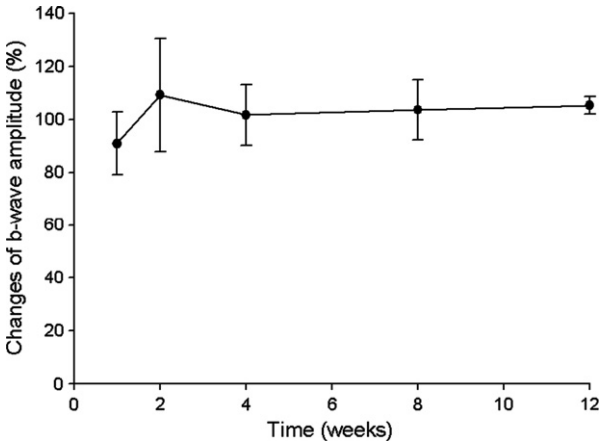

Fig. 10. The changes in scotopic b-wave amplitudes after the intrascleral implantation of the TA-loaded PLA implant. $p > 0.05$ by paired Student's t-test.

Few studies have been undertaken on the development of transscleral delivery devices for steroids, such as betamethasone [21,24] or triamcinolone [30]. Felt-Baeyens et al. [30] developed a scleral TA containing implant using a poly(methylidene malonate) (PMM2.1.2). They reported that implants were able to release significant concentrations of TA in the vitreous and the sclera throughout 5 weeks with good ocular biocompatibility. They used their TA implant as an episcleral implant. But in our study, we used intrascleral implantation because thinning of the sclera may enhance the drug permeation through the sclera [31].

3.4. Toxicity and biocompatibility

In the present study, slit lamp observation showed no significant inflammatory response at implantation sites; mild conjunctival injection was observed but disappeared at 1 week post-implantation (Fig. 8). Indirect ophthalmoscopy demonstrated no abnormal findings in retinas during the observation period. Intraocular pressure did not significantly change before and after implantation (Fig. 9, $p > 0.05$), and scotopic b-wave amplitude ratios before and after implantation were not significantly different (Fig. 10, $p > 0.05$). In histological study, retinas near implantation sites showed no histological abnormalities at 12 weeks post-implantation (Fig. 11a); a few neutrophils found around implantation sites were probably due to the suture material (Fig. 11b).

In the present study, a large amount of TA was detected in aqueous humor *in vivo*, and although intraocular pressures did not change significantly (Fig. 9), it might be expected that glaucoma and cataract, which are the main complications of intravitreal and of periocular TA injections, may also be induced by the devised TA implant. However, in the present study, implants were placed just 3 mm behind the limbus, and we consider that this distance should be increased clinically to prevent such complications because the concentration of the drug decreased with an increased distance from the implantation site [32].

The limitations of our study are that we did not measure systemic TA concentrations in rabbit to demonstrate the effectiveness of the high MW PLA coating and did not assess the possible toxic effect of TA on the RPE. Moreover, the rabbit sclera is very thin and the formation of intrascleral pockets may need particular surgical skills to

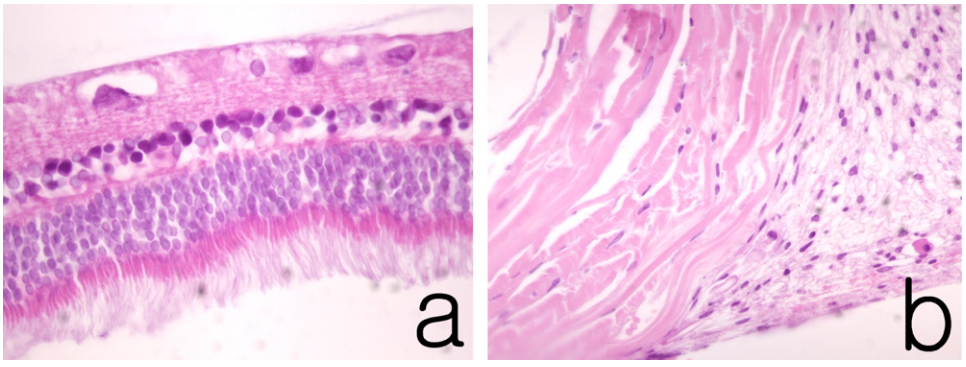

Fig. 11. Retina showing a normal architecture and no pathological finding by light microscopy at 12 weeks post-implantation (a: 400×). Compact scleral connective tissue was replaced by loose connective tissue and minor neutrophil infiltration was noted (b: 400×).

avoid sclera perforation or suprachoroidal placement of the TA implant. But the human sclera is thicker than that of the rabbit [13,33], and this procedure would be considerable easier.

The main advantage of our implant is that it could feasibly be used as an episcleral implant. Moreover, we should add that it contains a powdered pure crystalline form of TA that is free of preservatives, like benzyl-alcohol, which are known to be toxic to the retina [34].

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