EFFECT OF INTRAVITREAL TRIAMCINOLONE ACETONIDE ON HEALING OF RETINAL PHOTOCOAGULATION LESIONS

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Purpose: To evaluate the effect of intravitreal triamcinolone acetonide (TA) on healing of retinal photocoagulation lesions using drug and laser dosing typically employed in clinical practice.

Methods: Laser burns with a 267-μm retinal beam size at 532-nm wavelength were applied to 40 eyes of Dutch belted rabbits. Barely visible to intense lesions were produced with pulses of 5, 10, 20, and 50 milliseconds and power of 175 mW. Eyes received intravitreal injections of either 2 mg TA/50 μL or balanced salt solution administered either 1 week before or immediately after laser treatment. Lesion grades were assessed acutely ophthalmoscopically and by a masked observer histologically at 1, 3, 7, 30, and 60 days.

Results: Both TA groups demonstrated significant reduction in retinal thickness throughout follow-up compared with balanced salt solution groups ($P < 0.001$). The width of the lesions at 1 day after injection was not significantly different between groups. However, by 7 days, the lesions in balanced salt solution groups contracted much more than in the TA groups, especially the more intense burns, and this difference persisted to 2 months. The healing rate of the barely visible burns was not significantly affected by TA compared with the balanced salt solution control eyes.

Conclusion: Triamcinolone acetonide injection previously or concurrently with photocoagulation significantly decreases laser-induced edema but interferes with lesions healing, thereby leaving wider residual scarring, especially persistent in more intense burns.

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Triamcinolone acetonide (TA) is a corticosteroid commonly used in ophthalmology for a variety of indications including uveitis and retinal vascular disease because of several of its many pharmacologic properties including downregulation of inflammatory cytokines such as the interleukins and its inhibitory effects on vascular endothelial growth factor expression.[1] Intravitreal TA has been reported to reduce inflammation and secondary choroidal and macular edema by intravitreal injection immediately after conventional panretinal photocoagulation (PRP) or endo-PRP during vitrectomy.[2–4] Triamcinolone acetonide has also been used as primary treatment or combined with laser therapy for macular edema secondary to diabetes and retinal vein occlusion, including large, prospective, randomized trials for these indications by the Diabetic Retinopathy Clinical Research Network (DRCR) that has compared the outcomes between these modalities as well as potential dosing and timing interactions.[1,5,6]

Steroids are used in a number of other surgical fields and have been shown to delay wound healing,[7] prevent scar overgrowth, and limit scar contraction.[8] However, the effect of TA on healing of retinal laser

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burns has not been extensively investigated. One previous study has evaluated the effect of intravitreal TA on choroidal neovascularization using a well-established model of laser-induced rupture of Bruch membrane.[9] The authors analyzed the effects of intravitreal TA immediately after argon laser photocoagulation in mice and performed immunohistochemistry targeting angiogenesis.[10] They found that TA reduced the number of proliferating cells at 3 days and that TA-treated mice had more Terminal deoxynucleotidyl transferase dUTP nick end labeling-positive cells at Day 1. In addition, TA caused a decrease in the Von Willebrand factor (vWF)-positive cells, indicating reduced neovascularization. Expression of glial fibrillary acidic protein (GFAP) and glial activation were not affected. However, that study did not analyze the effects of TA on healing of the clinically relevant retinal burns over time. In the present study, we evaluate the effect of intravitreal TA on healing of the retinal photocoagulation lesions using a variety of drug and laser dosing regimens.

Material and Methods

Animals

Thirty-seven Dutch belted (pigmented) rabbits (weight 2–3 kg) were used in accordance with the Association for Research in Vision and Ophthalmology Statement Regarding the Use of Animals in Ophthalmic and Vision Research, after approval from the Stanford University's Animal Institutional Review Board.

Triamcinolone Acetonide

Fifty microliters of TA (Triesence; Alcon, Ft. Worth, TX) was centrifuged at 3,000*g* for 5 minutes. The supernatant (45 μL) was removed, and the TA was resuspended with 45 μL of balanced salt solution (BSS) (Alcon, TX). The concentration of TRIESENCE was 40 mg/mL. In humans, typically 4 mg or 100 μL of 40 mg/mL suspension is used for the treatment. The human vitreous volume is 5.2 mL; the rabbit vitreous volume is 2 mL, or 38%, of the human volume. To maintain a similar concentration per volume of the vitreous in rabbits, 2 mg of TA was applied in all experiments as a single intravitreal injection in a 50-μL volume.

Rabbits were randomized to one of four treatment groups: group SIM (simultaneous treatment) with either TA or BSS and group PRE (pretreatment) with either TA or BSS. In Group SIM, the rabbits received intravitreal injection immediately after retinal laser application. In Group PRE, the rabbits received intravitreal injection 7 days before the retinal laser application.

Laser System

The PASCAL laser system (Topcon Medical Laser Systems, Santa Clara, CA) provided 532-nm optical radiation from a diode-pumped, continuous wave, frequency-doubled Nd:YAG laser coupled into a multimode step index optical fiber. The exit surface of the fiber was imaged through the scanning system onto the retina with variable magnification, providing a variety of spot sizes with nominally flattop intensity profiles. A touch screen graphical user interface was used to control laser parameters including the spot size, laser power, pulse duration, and pattern geometry.

Retinal Laser Application

Rabbits were anesthetized using ketamine hydrochloride (35 mg/kg, intramuscular), xylazine (5 mg/kg, IM), and glycopyrrolate (0.01 mg/kg, IM) administered 15 minutes before the procedure and subsequently at half doses every 45 minutes of the procedure. Pupillary dilation was achieved by 1 drop each of 1% tropicamide and 2.5% phenylephrine hydrochloride. Topical tetracaine 0.5% was instilled in each eye before treatment.

A Mainster standard retinal laser contact lens (model no. OMRA-S, Ocular Instruments, Bellevue, WA) was used to focus the laser on the rabbit fundus. Taking into account the combined magnifications of the contact lens and rabbit eye of 0.66,[11] the aerial image of 400 μm corresponded to retinal spot size of 267 μm. Laser power was maintained at 175 mW for all lesions. The pulse duration of the laser varied from 5 milliseconds to 50 milliseconds to produce 4 different clinical grades of the laser lesions: 5 milliseconds (barely visible), 10 milliseconds (light), 20 milliseconds (moderate), and 50 milliseconds (intense). All lesions were graded by a single observer within 30 seconds after the treatment as described in a previous study.[12] Barely visible lesions were defined as a faint lightening of the fundus pigmentation. Light lesions were characterized by further blanching but without frank whitening. Moderate lesions exhibited definite retinal whitening without adjacent edema, whereas intense burns displayed central whitening and a halo of translucent edema. A pattern was developed in which moderate and intense burns were placed in a grid adjacent to light and barely visible lesions to facilitate later histologic localization of the lesions.

Intravitreal Injection

Intravitreal injection was performed by first cleansing the eye with a 1% solution of Betadine. A sterile 30-gauge hypodermic needle was inserted through the pars plana and visualized through an operating microscope. Fifty microliters was injected intravitreally, consisting of 2 mg of TA in either 50 μL of BSS or 50 μL of BSS. All injections were administered inferiorly to prevent obscuration of the subsequent laser application in the preinjection groups. All measurements and analysis were performed by researchers masked to the treatment the animal was receiving, and the syringes were labeled by an independent person with an alphanumeric coding system that was uncovered at the completion of the analysis. Postoperatively, the eye was rinsed with sterile BSS, 1 drop of topical ofloxacin and bacitracin/polymyxin B sulfate (500/10,000 units) were topically applied to the eye.

Retinal Histology

Rabbits were killed at 1 hour, 1 day, 1 week, 1 months, and 4 months post laser application with a lethal dose of intravenous Beuthanasia (Schering-Plough Animal Health Corp., Kenilworth, NJ) in the marginal ear vein (150 mg/kg, intravenous). Eyes were enucleated and fixed in 1.25% glutaraldehyde/1% paraformaldehyde in cacodylate buffer at pH 7.2 overnight at room temperature. Tissue was then postfixed in osmium tetroxide, dehydrated with a graded series of ethanol, infiltrated with propylene oxide and epoxy, embedded in an epoxy resin, and sectioned into 1-μm-thick sections. Samples were stained with toluidine blue and examined by light microscopy.[13]

By visually scanning the serial sections, the widest portion of the lesion corresponding to its geometric center was identified, photographed, and measured by the masked observer using ImageJ (NIH, Bethesda, MD). Burns were analyzed for each treatment group (4), time points (6), and pulse durations (4). Three measurements were performed for each lesion by a masked observer: the width of damage zone at the retinal pigment epithelium–photoreceptor junction ([a] in Figure 1), the width of the outer nuclear layer defect ([b] in Figure 1), and retinal thickness in the center of the lesion ([c] in Figure 1).

Statistical Analysis

Data are expressed as the mean and standard deviation. Statistical analysis using SPSS v.17 (SPSS, Inc) was performed with one-way analysis of variance, followed by the Bonferroni correction for multiple comparisons test when indicated. Because of multiple comparisons, differences were considered significant when P was <0.01.

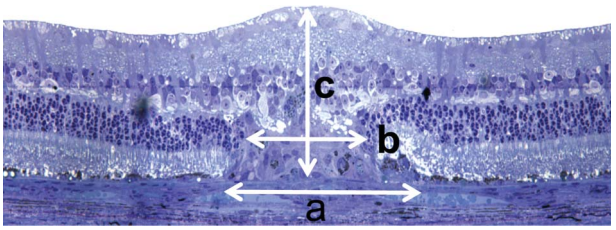

Fig. 1. Measurements of the retinal photocoagulation lesions: **a**, Width of the damage zone at RPE–photoreceptor junction; **b**, Width of the outer nuclear layer defect; **c**, Retinal thickness in the center of the lesion. RPE, retinal pigment epithelium.

Results

Forty-six eyes of 37 rabbits were studied. Ocular pigmentation appeared to be similar, although in rabbits injected with TA 1 week before laser therapy, there was slightly poorer visualization of the retina. Normal retinal thickness including retinal pigment epithelium was measured at least 1 spot diameter distant to the laser burn in 88 different histologic sections, and the average normal thickness was found to be 134.68 ± 8.85 μm.

Barely Visible Lesions

Ninety-three lesions of barely visible clinical grade were analyzed. Immediately after the laser treatment, no difference between TA and BSS groups could be observed ophthalmoscopically. The pretreatment TA group (pre-TA) had mean retinal thickness closer to normal values at 1 day (131 ± 6 μm) compared with simultaneous injection of TA (sim-TA) (149 ± 7 μm) and BSS groups (153 ± 5 and 157 ± 8 μm; $P < 0.001$). There was no difference between the 2 TA groups in retinal thickness at 3, 7, and 30 days. However, at 60 days, sim-TA demonstrated larger reduction in retinal thickness compared with pre-TA and both BSS groups ($P < 0.01$; Figure 2B).

At 1 day and after 60 days, there was no statistically significant difference between groups in the width of the damage zone at the retinal pigment epithelium–photoreceptor junction or outer nuclear layer (ONL) defect (Figure 2A and Table 1). Mean lesion diameter for pre- and sim-TA groups was 151 ± 16 and 158 ± 10 μm at 1 day, respectively, compared with 40 ± 10 and 57 ± 12 μm at 2 months. With pre- and sim-BSS, the lesion width was 157 ± 6 and 156 ± 10 μm at 1 day compared with 51 ± 7 μm and 52 ± 7 at 2 months, respectively ($P = 0.12$).

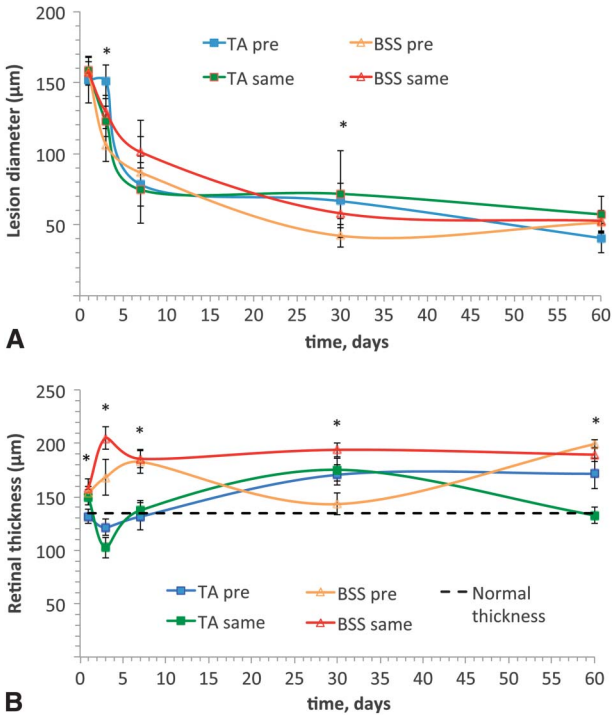

Fig. 2. **A**, Lesion diameters (μm) and (**B**) retinal thickness (μm) of barely visible burns (5 milliseconds). Data are presented as mean ± SD. Dashed line represents normal value of retinal thickness. *$P < 0.001$.

Light Lesions

Ninety lesions of the light clinical grade were analyzed (Figure 3). Ophthalmoscopically, the acute laser lesions with TA and BSS injections were indistinguishable. At 1 day, retinal thickness in sim-TA group was significantly lower than pre-TA and both BSS groups (139 ± 5, 163 ± 3, 166 ± 14, and 174 ± 5 μm, respectively; $P < 0.001$). After 2 months, the retinal thickness in the sim-TA group was closest to normal and significantly lower than pre-TA and BSS pre- and sim- groups (111 ± 27, 171 ± 10, 190 ± 10, and 178 ± 11 μm, respectively, as shown on Figure 4B; $P < 0.001$).

Although there was a trend, no statistically significant difference in lesion diameter was identified between TA and BSS groups after 1 day ($P = 0.02$). However, after 3, 7, and 30 days, both TA groups had significantly wider lesions and ONL defects compared with BSS groups ($P < 0.001$), after 2 months, although the differences diminished and became insignificant ($P = 0.28$; Figure 4A and Table 1).

Moderate Lesions

A total of 104 burns with moderate clinical grade were analyzed. Retinal thickness of TA-injected eyes

Table 1. Outer Nuclear Layer Defect Width (μm)

	1 Day	3 Days	7 Days	30 Days	60 Days
BV	119.63 ± 9	111.89 ± 8*	68.06 ± 7*	44.78 ± 10	26.00 ± 5
TA pre	122.63 ± 16	91.28 ± 6*	62.66 ± 13*	42.38 ± 9	41.54 ± 2
TA same	107.56 ± 24	66.15 ± 16	37.75 ± 17	27.49 ± 10	37.00 ± 13
BSS pre	105.58 ± 15	39.81 ± 0.9	40.06 ± 7	40.76 ± 10	23.25 ± 3
BSS same					
P	0.27	<0.001	<0.001	0.04	0.02
Light	150.73 ± 7	122.03 ± 17*	83.43 ± 1*	90.19 ± 25*	57.89 ± 16
TA pre	141.17 ± 13	113.74 ± 7*	91.24 ± 7*	89.92 ± 18*	61.88 ± 26
TA same	153.30 ± 10	109.17 ± 20*	62.90 ± 8	50.81 ± 8	61.67 ± 21
BSS pre	136.55 ± 7	45.86 ± 9	37.54 ± 9	42.29 ± 13	38.45 ± 21
BSS same					
P	0.04	<0.001	0.001	<0.001	0.28
Mod	162.72 ± 4*	142.21 ± 15*	122.29 ± 1*	133.70 ± 3*	96.83 ± 24
TA pre	166.69 ± 11*	112.30 ± 14	110.85 ± 19	109.17 ± 16*	110.51 ± 27*
TA same	145.56 ± 15	112.08 ± 35	55.44 ± 24	53.84 ± 19	56.40 ± 16
BSS pre	125.60 ± 15	61.65 ± 7	60.75 ± 11	51.67 ± 4	68.46 ± 22
BSS same					
P	<0.001	0.004	0.001	0.001	0.002
Intense	217.57 ± 18*	198.92 ± 19*	132.30 ± 7	147.83 ± 14*	122.41 ± 18
TA pre	221.36 ± 14*	186.86 ± 27*	136.91 ± 16	146.09 ± 15*	141.12 ± 40*
TA same	186.46 ± 16	176.11 ± 16	88.78 ± 57	109.42 ± 43	76.66 ± 32
BSS pre	166.59 ± 33	125.48 ± 17	104.27 ± 22	83.93 ± 27	86.26 ± 19
BSS same					
P	<0.001	0.001	0.16	0.002	0.004

BV, barely visible; Mod, moderate.
Data are presented as mean ± SD.
*$P < 0.01$.

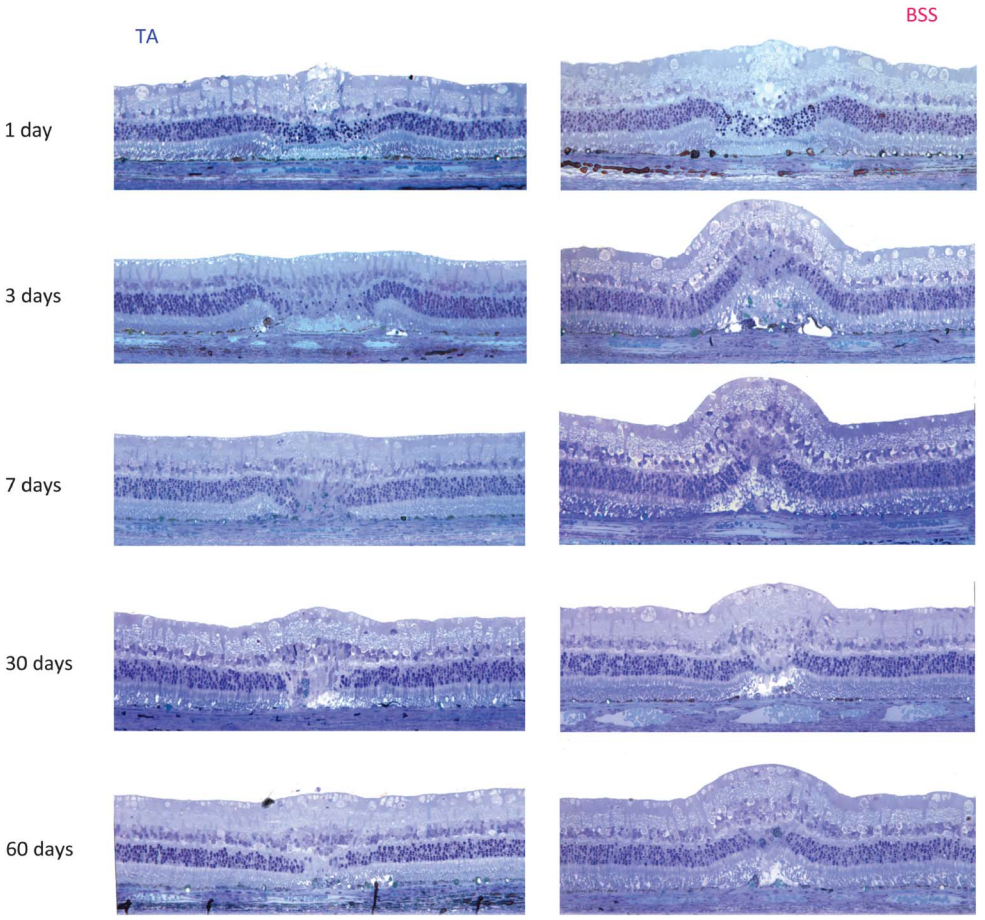

Fig. 3. Light microscopy of the light laser lesions (10 milliseconds) with simultaneous injection of either triamcinolone (left) or BSS (right) over 60 days of follow-up. Note the significant increase in retinal thickness in BSS groups compared with TA-treated retina from 3 days to 2 months.

was lower than BSS groups throughout the follow-up period. At 2 months, only the sim-TA group showed a statistically significant difference compared with both BSS groups: 118 ± 46, 153 ± 9, 185 ± 13, 177 ± 1 μm for sim-TA, pre-TA, BSS pre- and sim-, respectively ($P = 0.001$; Figure 5B).

The lesion width at the retinal pigment epithelium–photoreceptor junction was similar in TA and BSS groups at 1 or 3 days. However, the ONL defect was significantly larger in both TA groups at 1 day, and with pre-TA after 3 days, compared with BSS groups (Table 1). Lesion diameters and ONL defects of TA groups were significantly larger than BSS groups after 7, 30, and 60 days, with the final diameters of 126 ± 29, 150 ± 15, 83 ± 29, and 96 ± 34 μm for pre-TA, sim-TA, pre-BSS, and sim-BSS, respectively ($P = 0.004$; Figure 5A).

Intense Lesions

A total of 109 burns with moderate endpoint were analyzed. Triamcinolone acetonide groups had lower retinal thickness compared with BSS groups after 1, 3, 7, and 30 days ($P < 0.001$). However, at 60 days, no statistically significant difference between the groups was detected (Figure 6B; $P = 0.35$).

No difference in lesion width between TA and BSS groups was distinguishable at 1, 3, and 7 days after laser treatment ($P > 0.05$; Figure 6A). However, the ONL defect was significantly larger for both TA groups after 1, 7, 30, and 60 days compared with BSS groups ($P < 0.001$). At 30 days, sim-TA group showed significantly larger lesion diameter compared with pre-TA and both BSS groups, as shown on Figure 6A. At 60 days, both TA groups had significantly wider lesions compared with BSS groups: 186 ± 13, 184 ± 27, 102 ± 40, 125 ± 24 μm for pre-TA, sim-TA, pre-BSS, and sim-BSS, respectively ($P < 0.001$).

Discussion

Because laser and TA are commonly used sequentially or concurrently in clinical practice, this study has potentially important implications for practicing ophthalmologists. It demonstrates that in rabbits, TA decreases laser-induced edema but restricts the natural contraction and healing of moderate and intense burns,

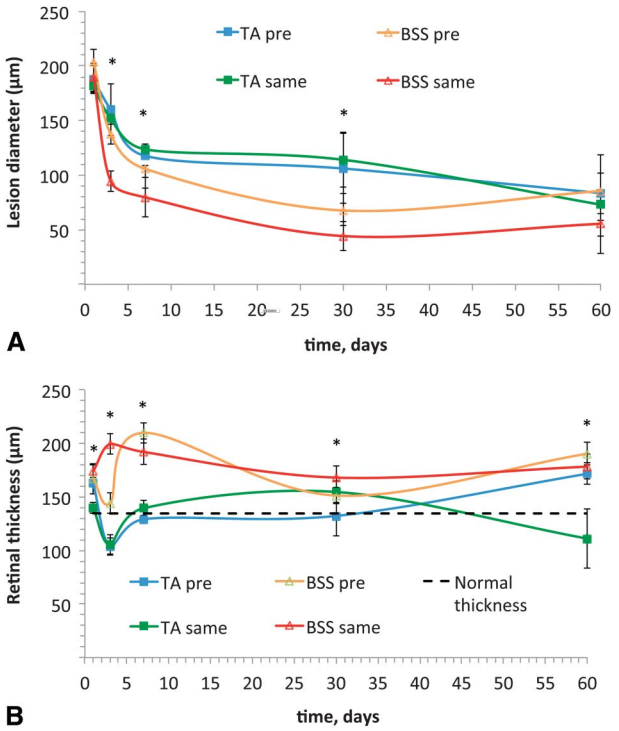

Fig. 4. **A**, Lesion diameters (μm) and (**B**) retinal thickness (μm) of light burns (10 milliseconds). Data are presented as mean ± SD. Dashed line represents normal value of retinal thickness. *$P < 0.01$.

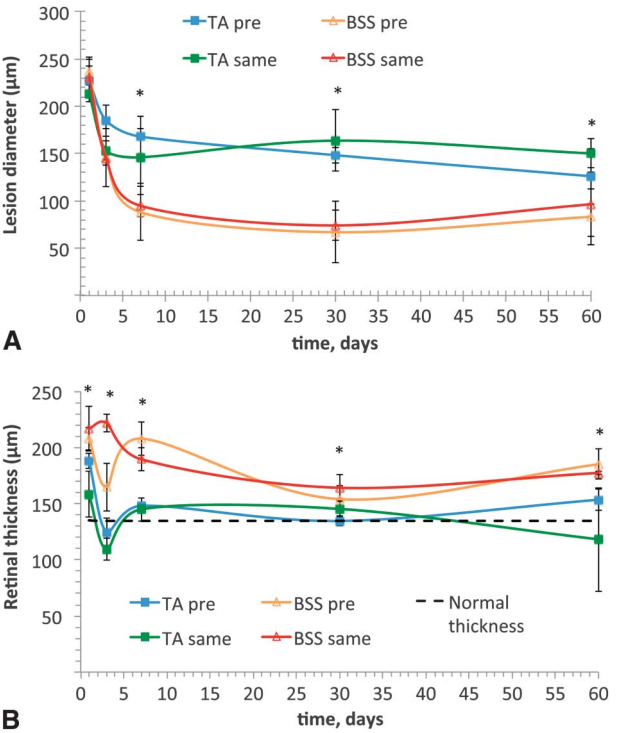

Fig. 5. **A**, Lesion diameters (μm) and (**B**) retinal thickness (μm) of moderate burns (20 milliseconds). Data are presented as mean ± SD. Dashed line represents normal value of retinal thickness. *$P < 0.01$.

although this effect was not significant for barely visible burns.

The drug dosages and laser regimens used in this study correspond to the parameters often used in clinical practice. Although concurrent intravitreal TA is not typically used in patients undergoing conventional PRP, it is not uncommon for patients undergoing PRP as part of pars plana vitrectomy for the complications of proliferative diabetic retinopathy. Similarly, in clinical practice as well as in a number of the DRCR trials for the treatment of diabetic macular edema, patients may receive an intravitreal injection of steroid followed by focal or grid photocoagulation.[4,5] As a result, the impact of concurrent or pretreatment with steroids in patients undergoing laser photocoagulation is a clinically relevant question that needs to be well understood.[6] In this study, we found that TA causes a significant decrease in retinal thickness at the site of burns at all time points measured for barely visible, light, and moderate clinical grades. This effect might be because of triamcinolone's ability to decrease vascular permeability, thus reducing edema and subsequent distortion of the retina.[14]

Restoration of retinal morphology after laser photocoagulation has been demonstrated in several animal studies.[15,16] This effect has been attributed to activation of Müller cells and migration of photoreceptors.[15] Triamcinolone acetonide treatment appears to modify this process, resulting in wider lesions, at least up to 2 months in TA-treated eyes, compared with BSS treatment, particularly for more intense laser burns. However, for barely visible burns, the difference in lesion width was not statistically significant, suggesting that TA does not significantly interfere with retinal restoration in very mild lesions. For more intense laser lesions, lesion size appears to stabilize by 1 week after laser application, and thus modification of the inflammatory cascade by TA even transiently around the time of laser application could result in permanent changes in the lesion size and swelling.

The underlying mechanism of the TA effect on healing processes in the retina is unknown. Because corticosteroids are used for preventing scarring or overgrowth, one could assume that inhibition of such processes through modulation of glial cell activation could also decrease contraction of retinal lesions after thermal injury.[17] Immunohistochemical analysis of glial cell activation could assist in understanding the cellular effects of TA on retinal healing.

There were very few differences between the two TA groups (pretreatment and simultaneous): retinal thickness was lower in (A) pre-TA group of barely

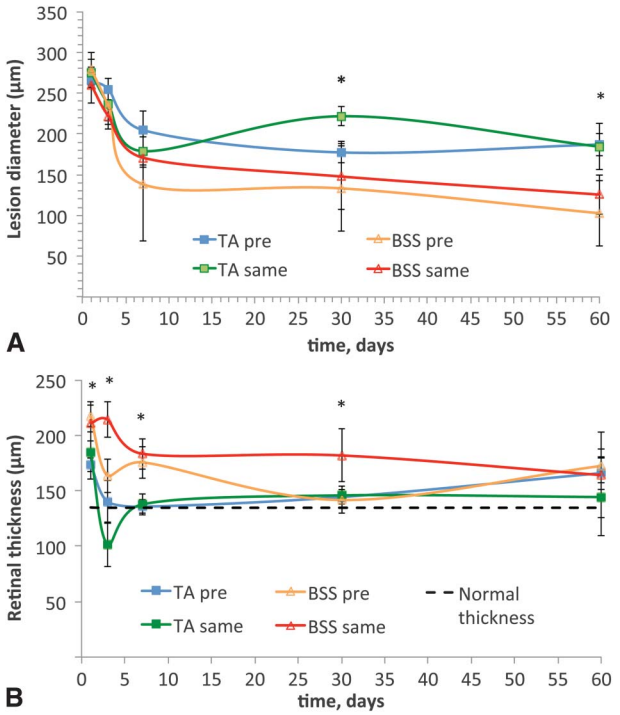

Fig. 6. **A**, Lesion diameters (μm) and (**B**) retinal thickness (μm) of intense burns (50 milliseconds). Data are presented as mean ± SD. Dashed line represents normal value of retinal thickness. *$P < 0.01$.

visible burns at 1 day and (B) in the sim-TA group of barely visible and light burns at 2 months. This suggests that in clinical settings, the two may be quite similar. Indeed, clinical studies of retinal laser combined with intravitreal steroids have not demonstrated a significant difference between pretreatment and concurrent treatment in terms of its effectiveness in reducing retinal thickness or visual improvement.[3,18]

As with any animal study, there are some caveats to consider when applying these results to humans. Rabbits have a merangiotic vasculature, whereas humans have a holangiotic. We also used relatively young rabbits with a formed vitreous in which we could often see the TA injection over a month later. In contrast, in adult humans with vitreous syneresis that are treated with TA, the drug may be cleared more rapidly. In clinical practice, TA is sometimes used to reduce retinal edema in pathologic conditions and thus decreases laser scattering in the retina, improving its uptake. We were unable to test this condition because our animal model had neither diabetes nor baseline edema. Additionally, pretreatment with TA resulted in slightly poorer visualization and consequently potentially less effective laser uptake in the retina, although no difference was noted in the initial lesion size as measured histologically.

Application of TA to the lightest burns appeared to have the most favorable risk/benefit ratio because it reduced retinal edema secondary to photocoagulation but did not appear to have a negative effect on lesion contraction over time. The impact of other forms of pharmacologic therapy on retinal wound healing after laser injury including vascular endothelial growth factor inhibitors remains poorly understood and a potential subject for future study.

Key words: laser photocoagulation, triamcinolone acetonide, retinal plasticity, wound healing, photoreceptors.

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