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Laser-Activated Corneal Adhesive: Retinal Safety in Rabbit Model

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Purpose: The purpose of this study was to investigate whether laser irradiation, used to activate an adhesive for sealing penetrating corneal incisions, causes any ophthalmoscopically or histologically visible retinal changes.

Methods: Baseline fundus assessment was conducted prior to laser irradiation of eyes of pigmented Dutch Belted rabbits. Treatment group was 18 eyes with the corneal adhesive activated in situ by a near infrared laser (125 mW for 45 seconds). The positive control group was 18 eyes, each irradiated for 60 seconds at 375, 500, 625, and 750 mW at different retinal locations. Unexposed regions of the retina were used as negative internal control. Ophthalmoscopic assessment was conducted immediately after laser exposure and prior to euthanasia. Retinas were histologically assessed at 0, 3, 72, and 168 hours after treatment.

Results: No ophthalmoscopically or histologically visible retinal changes were observed in the treatment group immediately, nor up to 168 hours after laser irradiation. In the positive control group, the incidences of ophthalmoscopically visible retinal lesions increased with irradiation power: 5.6% at 375 mW, 16.7% at 500 mW, 44.4% at 625 mW, and 50% at 750 mW. Histologically, retinal damage was observed as coagulative necrosis to all layers of the neural retina, including the retinal pigment epithelium.

Conclusions: The laser irradiation process used in the corneal adhesive technology did not cause any ophthalmoscopically or histologically visible retinal changes in the in vivo pigmented rabbit model. Prolonged exposure with this laser and at higher power can cause coagulative necrosis to the retina.

Translational Relevance: The corneal adhesive can be applied in humans without causing laser retinal damage.

Introduction

We have developed a laser-activated thin-film adhesive technology to seal penetrating corneal incisions.[1–4] Data from ex vivo bovine and in vivo rabbit corneal models demonstrated that this adhesive tolerated average burst pressures of 239.2 ($\pm$72.4) and 98.0 ($\pm$17.0) mm Hg for 2 mm incisions, respectively.[1,4] Adhesion activation requires the use of a near-infrared (810 nm) laser at 125 mW, for approximately 45 seconds, near light sensitive ocular tissue. Previous studies showed no corneal tissue damage as a consequence of this irradiation,[1,2,4] The current study investigates the impact of this laser application on the retina.

Laser-tissue interactions depend on the wavelength, power, duration of exposure, the heat capacity of the exposed tissue, and the use of focusing optics.[5] Infrared laser is particularly useful clinically as it has good transmission through hemorrhagic media opacities and nuclear sclerotic cataract, while having negligible absorption by macular xanthophyll.[6,7] For over 3 decades, near infrared (NIR) lasers of wavelengths 790 to 840 nm have been used in ophthalmic therapies for retinal vascular conditions, such as proliferative diabetic retinopathy, exudative retinopathy, and retinal vein occlusions.[8] The

mechanism of action is the absorption and conversion of laser energy by melanin within the retinal pigmented epithelium (RPE) and choroid, into thermal energy and subsequent tissue coagulation.[9] Studies in humans have shown that threshold retinal lesions were achieved at irradiances between 95.4 W/cm^2 and 191 W/cm^2, with non-Caucasian patients requiring lower irradiances due to differences in fundus pigmentation.[9]

At 810 nm, the radiant energy absorption by the collective pre-retinal clear media (cornea, crystalline lens, and vitreous) is 4.5%.[10] In laboratory studies, most of the radiant energy carried by the 810 nm laser was selectively absorbed by melanin pigments within the RPE and the choroid.[5,11] Eight hundred ten nm irradiation was also absorbed by hemoglobin and the photoreceptors, but they collectively absorbed less than 15% of the total energy.[11,12] At the retina, a computational model suggested that a temperature rise from 810 nm laser exposure was 65% attributable to RPE and 35% to the choroid.[13] Overall, any adverse effect of 810 nm laser eye exposure would likely be found in the RPE layer of the retina.[14]

Laser thermal energy can spread three-dimensionally by conduction, resulting in a thermal blooming effect, whereby the coagulation zone extends beyond the boundary of the applied laser spot.[5] Pulsed lasers have been developed to limit heat diffusion within the region of exposure.[15] Desmettre et al. demonstrated using an 810 nm laser that, despite requiring a higher power (1800 mW) over 0.3 milliseconds, compared to 300 mW over 0.2 seconds, to create a visible retinal lesion in humans, the overall energy delivered was similar (54 mJ and 60 mJ, respectively).[16] The shorter duration laser had a 3.7 times higher safety margin than the longer exposure laser.[16]

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) provides guidelines for Maximal Permissible Exposure (MPE) of safe laser exposure for human eyes.[11] Although the calculated exposure limit for our laser of 6.1 mW/mm^2 exceeds the ICNIRP recommended limit by 20 times,[11] Desmettre et al. have suggested that the ICNIRP guidelines are deliberately conservative.[16] The chromophore (Indocyanine Green [ICG]) within our adhesive traps the 810 nm irradiation and attenuates the power entering the eye, with the laser power reduced to 40 to 50 mW after transmission through the adhesive. Given the blood perfusion of the choroid serves as a heat capacitor to dissipate thermal energy,[17] it is unclear whether there will be any laser-related retinal damage from the use of our parameters.

To assess for any putative retinal damage, we utilized a pigmented in vivo rabbit model. The pigmented rabbit is a well-established retinal model that has a 3 times lower damage threshold to 810 nm radiation compared to humans.[18] Studies have shown that with 60 seconds exposure during transpupillary thermotherapy (TTT) for choroidal melanoma, threshold lesions (2 mm spot diameter) were created at 148 mW in rabbits, whereas threshold lesions were created at 800 mW, with 3 mm spot diameter in humans.[19,20] In order to create a positive control with a spread of discernible laser damage for comparison, we initiated retinal irradiation at 375 mW, with variation of subsequent laser power pending any obvious laser lesions. Laser damage not immediately visible had shown delayed histological changes, such as disorganization of the photoreceptor layer, collapse of RPE, and reduction of RPE pigmentation up to 1 week after exposure.[21] In order to assess for any delayed damage, we utilized an in vivo model for this study.

Materials and Methods

Animals and Anesthesia

A total of 18 pigmented Dutch Belted rabbits were bred for this study (Piper's farm, Cowra, New South Wales, Australia). Rabbits were of mixed genders, used at 5 months old to ensure head maturity, weighing between 1.26 and 1.70 kg at the time of the procedure.[14] Rabbits were acclimatized in our facility for at least 1 week prior to any procedure, and had unlimited access to chow and water. All animal procedures adhered to the ARVO statement for the Use of Animals in Ophthalmic and Vision Research. Institutional animal ethics committee approval (University of Sydney AEC 2019/1607) was obtained prior to any procedures. In accordance with the reduction principle for ethical use of animals, the right eyes ($n = 18$) were used for delayed timepoints of 3, 72, and 168 hours, whereas the left eyes ($n = 18$) were used for timepoint 0 hours prior to euthanasia.

All procedures were performed aseptically under an operating microscope. Sterile drapes, gloves, and surgical gowns were used. A sterile wire eyelid speculum was used to open the palpebral fissure. Prior to the procedure, topical oxybuprocaine hydrochloride (0.4%), tropicamide sulphate (1%), phenylephrine hydrochloride (2.5%), and chloramphenicol (0.5%) were instilled over the corneal surface and into the conjunctival fornix. All eyedrops were single-use Minims (Bausch & Lomb).

General anesthesia was provided by a specialist team of veterinarians. Premedication was a combined

intramuscular injection (IM) of methadone (1 mg/kg), dexmedetomidine (50 mcg/kg) and midazolam (0.5 mg/kg). The induction agent used was intravenous (IV) propofol (6 mg/kg), and IV rocuronium (10 mcg/kg) was used as a paralytic agent to ensure no eye movements. Maintenance of anesthesia was by inhalational isoflurane (1.5 to 3.0%). Atipamezole (0.5 mg) was given IM as a sedation reversal agent. A topical buprenorphine (25 mcg/hr) patch was applied to all rabbits for analgesia. Rabbits' welfare was monitored hourly until full recovery from anesthesia, then twice daily for the first 3 days, and daily thereafter until the planned end point. Supplemental anesthetic/analgesic drugs were used at the discretion of the veterinary anesthetist for managing animal welfare.

Treatment Group

Thin-film adhesives were obtained sealed in a foil pack from Repartech Pty Ltd (New South Wales, Australia).[22] Adhesives were cut to size (4 × 6 mm oval, area of 19 mm^2) using microsurgical scissors prior to use and had an average thickness of 25.10 μm (±0.86 μm). A continuous-wave Gallium-Aluminum-Arsenide (GaAlAs) diode laser (MDL-III-808-1W, Changchun New Industries Optoelectronics Tech Co., Ltd., China) was used for adhesion activation. The laser wavelength was 810 nm, power of 125 mW, and spot diameter of 1 mm (area 0.79 mm^2). Central corneal epithelium was mechanically debrided to reveal a 4 × 6 mm corneal stroma. The adhesive was applied directly over debrided area. The laser was then applied 1 to 2 mm perpendicularly over the adhesive using a hand-held fiber-optic probe moving at a speed of 1 mm/sec. The laser application took approximately 45 seconds and delivered a total of 5.6 joules of energy. Adhesion was visually confirmed by a gentle warping of the adhesive onto the corneal surface and a mild whitening of the translucent green adhesive. The adhesive was removed prior to fundoscopic assessment.
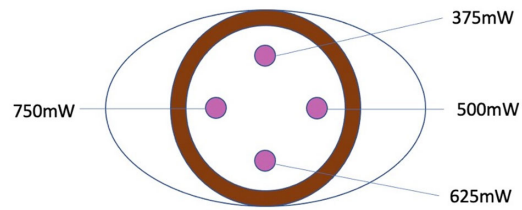

Figure 1. Schematic diagram showing the relative positions of each laser application on the cornea in the positive control group.

Positive Control Group

Irradiation with the same laser (810 nm) using different output powers were stationarily applied for 60 seconds, 1 to 2 mm perpendicularly over the ocular surface without the adhesive. Powers of 375, 500, 625, and 750 mW were applied at 12, 3, 6, and 9 o'clock locations, as per Figure 1 below. Fundoscopic assessments were conducted after each application. The Table below summaries the 810 nm laser parameters used in both treatment and positive control groups with a comparison against laser parameters reported in a similar study by Kandulla et al.[19]

Fundoscopic Assessment

A direct ophthalmoscope (oDocs nun, oDocs Eye Care, New Zealand) with smartphone (iPhone XR, Apple Inc.) attachment capability, was used to assess the fundus of each eye. The fundus was assessed preprocedure (baseline), immediately after each laser exposure (0 hour), and prior to euthanasia at each planned timepoint. A video recording was created for each fundoscopic assessment, and the captured images were screened by frames for visible laser lesions.

Timepoints for Histology and Euthanasia

Rabbits were euthanized at 3, 72, and 168 hours post laser exposure, with an overdose of IV sodium pentobarbitone (100 mg/kg). Extinction of life was

Table. A Table Comparing Laser Parameters of the Adhesive Group, Positive Control Groups and Published Data From Kandulla et al.[19]

Laser Parameter	Treatment Group	Positive Control Group				Kandulla et al.
Power (mW)	125	375	500	625	750	148
Beam spot area (mm^2)	0.79	0.79	0.79	0.79	0.79	3.14
Irradiated area (mm^2)	18.85	0.79	0.79	0.79	0.79	3.14
Duration (seconds)	45	60	60	60	60	60
Irradiation (J)	5.63	22.50	30.00	37.50	45.00	8.88
Fluence (J/mm^2)	0.30	28.48	37.97	47.47	56.96	2.83

confirmed by no heartbeat on auscultation and a fixed dilated pupil. Six right eyes were collected at each timepoint for treatment group ($n = 3$) and positive control group ($n = 3$). A total of 18 left eyes were collected for timepoint 0 hour.

Histological Analysis

After euthanasia, the posterior eye cups were gently dissected and immediately transferred into 10% neutral buffered formalin (NBF) and fixed for 10 hours. Fixed retinal tissue was serially dehydrated through increasing concentrations of ethanol (50 to 100%) using an automatic tissue processor (Excelsior ES tissue processor, Thermo Scientific, USA) and then cleared in xylene.[23] Retinal tissues were trimmed to localize regions of interest before embedding in paraffin wax. A manual microtome (Reichert-Jung Histocut 820, Leica, Germany) was used to produce 7 μm sections for histological analysis. Tissue sections containing regions of interest were screened under dark-field illumination.

Representative tissue sections were de-paraffinized and hydrated to distilled water for Periodic acid-Schiff (PAS) staining, as per Lovicu et al.[23] Sections were left in 0.5% periodic acid solution for 10 minutes, rinsed with distilled water, and stained with Schiff's reagent for 30 minutes. Sections were then rinsed in sodium metabisulphite for 2 minutes, and water for 5 minutes prior to counterstaining with hematoxylin. One percent of lithium carbonate was applied for 1 second before further rinsing in distilled water. Sections were then dehydrated through increasing concentrations of ethanol (50 to 100%), cleared in xylene, perma-

nently mounted using DePex mounting medium, and then viewed and photographed using a Leica DMLB microscope (Leica DFC-280; Wetzlar, Germany).

Results

Ophthalmoscopic Assessment

Ophthalmoscopically visible laser retinal lesions were not observed in any of the 18 eyes from the treatment group at timepoint 0 hour. In contrast, ophthalmoscopically visible laser lesions were detected in the positive control group in 5.6% locations irradiated at 375 mW, 16.7% at 500 mW, 44.4% at 625 mW, and 50% at 750 mW ($n = 18$; Fig. 2). Figure 3 demonstrates a representative laser retinal lesion from the positive control group.

The fundus of the 9 eyes from the treatment group showed no delayed ophthalmoscopically visible retinal lesions over 168 hours. Only 2 eyes in the positive control group developed delayed retinal lesions visible at 72 and 168 hours post-exposure.

During the course of our study, the presence of visible retinal lesions was inconsistent among the rabbits even at our highest power setting (750 mW). Although rabbits were randomly distributed at the beginning of the study, we noticed that all visible retinal lesions were only in the positive control group and predominantly (9 out of 10) with rabbits possessing black/white coats. Ophthalmoscopic findings supplementary file 1 was included to demonstrate representative ophthalmoscopic,
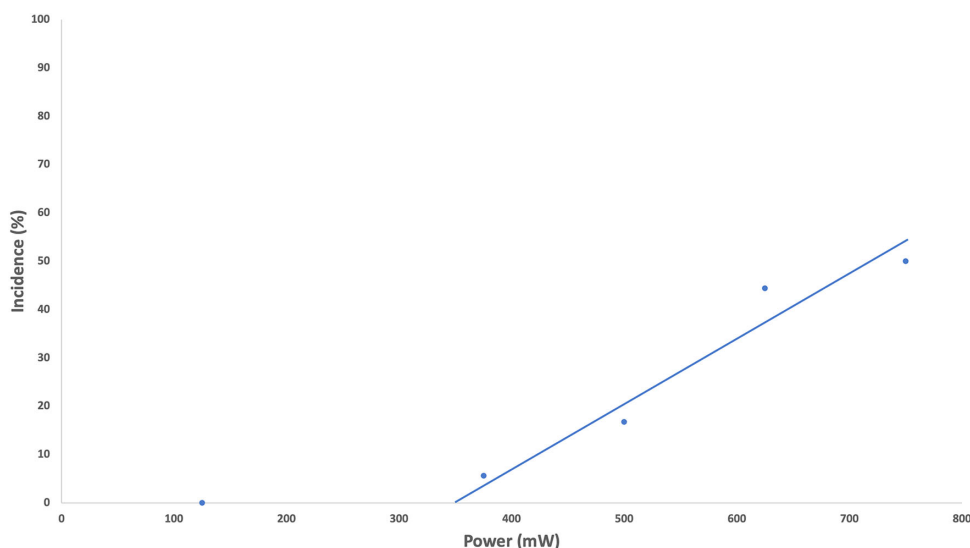

Figure 2. Graph demonstrating the incidence of ophthalmoscopically visible retinal lesions induced by different 810 nm laser powers, 125 mW (treatment group), 375 mW, 500 mW, 625 mW, and 750 mW, at timepoint 0 hour. $R^2 = 0.9401$.
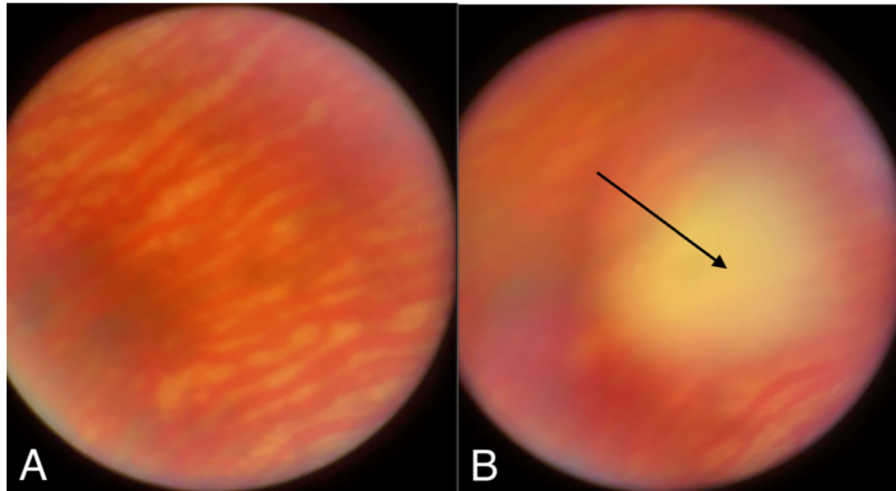
Figure 3. Representative fundoscopic images of (**A**) preprocedure baseline and (**B**) a visible laser induced retinal lesion, see arrow (750 mW, same eye, positive control group).
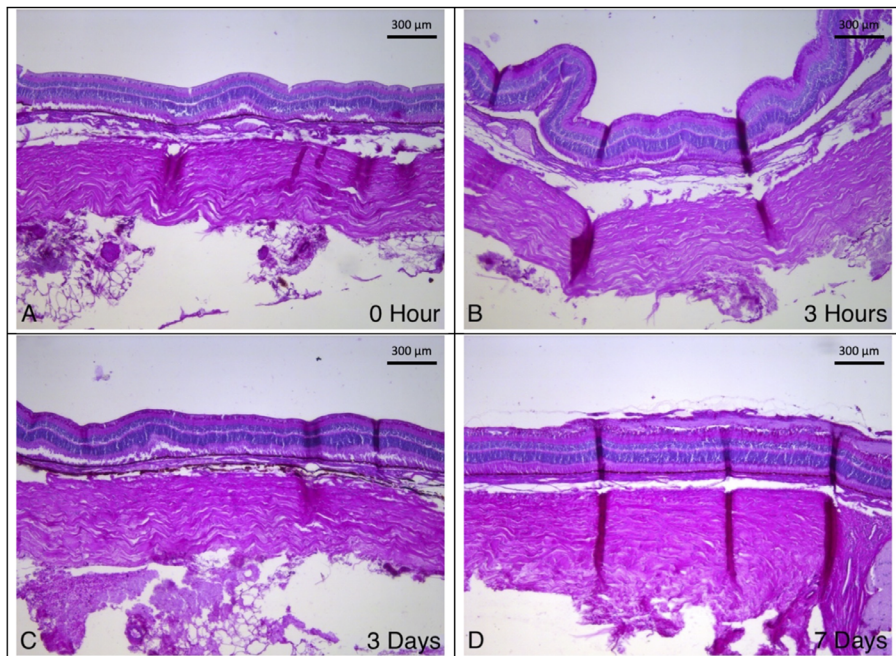

Figure 4. Representative retinal histologic sections from pigmented Dutch Belted rabbits exposed to laser required to activate the adhesive (treatment group) at 0 hour (**A**), 3 hours (**B**), 3 days (**C**), and 7 days (**D**).

postmortem, and histologic findings from the entire study.

Histological Assessment

Histologically, retinas from the treatment group did not show any immediate or delayed histologic changes throughout the study. Untreated areas of the same eyes were used as negative internal controls for comparison.

The temporal progression of retinal histologic findings from the treatment group is demonstrated in Figure 4.

In the positive control group, ophthalmoscopically visible retinal lesions corresponded to coagulative tissue necrosis, with ejection of retinal tissue and fragmentation of all neural retinal layers. Large vacuoles were observed in the ganglion cell layer, as well as thickening of the RPE layer, up to 72 hours, and this was followed by splaying and scattering of melanin pigments within the region of coagulative necrosis.
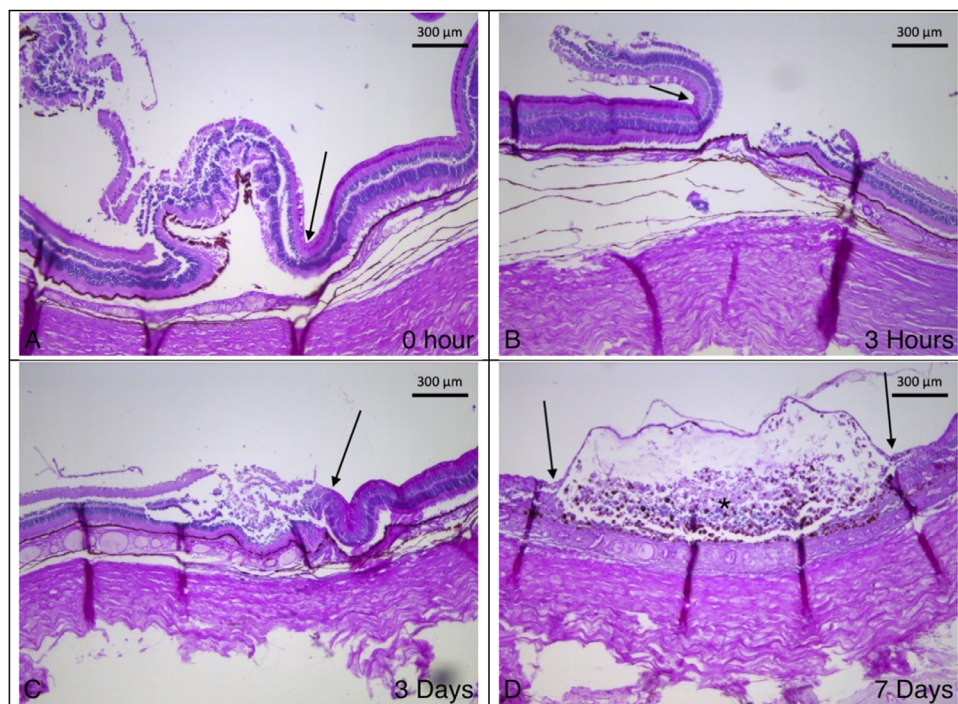
Figure 5. Representative retinal histologic sections highlighting the transition zone (*black arrows*) between laser damaged retina and healthy retina from pigmented Dutch Belted rabbits from the positive control group at 0 hour (**A**), 3 hours (**B**), 3 days (**C**), and 7 days (**D**). The asterisk (*) in **D** indicates coagulative necrosis with disorganization of all neural retinal layers.

The photoreceptor layer remained unaffected up to 72 hours but was observed to disintegrate with the healing response after 168 hours. Between 72 and 168 hours following laser injury, there was sloughing of the entire devitalized retina, leaving only the underlying Bruch's membrane and choriocapillaris intact (Fig. 5D). There was also suggestion of thermal coagulation of collagen fibers in the sclera directly over the laser exposure zone. Figure 5 demonstrates the temporal progression of histologic changes in the positive control group. Further histological findings were demonstrated in Histological findings supplementary file 2.

Discussion

Our study clearly demonstrates that the laser irradiation parameters used to activate the corneal adhesive[1,4] did not result in any ophthalmoscopically or histologically visible retinal lesions immediately after, or up to 168 hours after exposure, in the pigmented Dutch Belted in vivo rabbit model.

Given the 3-fold higher safety margins for 810 nm irradiation in humans,[18] application of this laser to activate the adhesive in sealing penetrating corneal incisions is highly unlikely to cause any discernible

retinal damage in humans. In the present study, a 95-fold increase in fluence showed only a 5.6% incidence of lesions immediately after irradiation, and with no additional lesion development 168 hours after treatment (see Table). Tissue damage presented as coagulative necrosis in all layers of the neural retina, including the RPE.

Our results were consistent with the findings from a transpupillary thermotherapy study for choroidal melanoma, whereby Kandulla et al. created retinal threshold lesions in a pigmented rabbit model using an 810 nm laser at 148 mW with a 2 mm spot diameter for 60 seconds (2.83 J/mm^2).[19] In our study, only 1 lesion out of 18 eyes was observed with a laser power of 375 mW with a 1 mm spot diameter for the same duration (28.48 J/mm^2). A comparison between the laser parameters used by Kandulla et al. and our study was demonstrated in the Table above. The incidence of retinal lesions increased when our laser power was increased, suggesting a dose-related response to injury (see Fig. 2). The well-demarcated, round-shaped, blanched retinal lesions in our positive control group resembled those reported in pan-retinal photocoagulation for proliferative diabetic retinopathy in humans.[12] In the current study, we also observed a higher incidence of retinal lesions in rabbits with black/white fur than those with grey/white or brown/white fur.

Although our study was not powered to investigate this observation, previous studies in humans had confirmed that non-Caucasian patients required lower irradiances for retinal threshold lesions due to differences in fundus pigmentation.[9]

In addition to a 10-fold lower fluence compared to that used in the Kandulla et al.[19] study (see the Table above), the laser in the treatment group was applied to an adhesive film designed to absorb irradiation. Preliminary studies showed a reduction in power from 125 to 40 to 50 mW after transmission through the adhesive. Vincelette et al. have reported a protective thermal lensing effect in ocular media when exposed to continuous wave NIR laser of wavelengths between 1150 nm and 1350 nm.[24] Thermal lensing enlarges the retinal spot size, thereby reducing laser intensity at the retina.[24] Our observed retinal lesions in the positive control group were larger than the 0.79 mm^2 laser beam spot, possibly due to thermal lensing and thermal blooming from heat dissipation within the tissue.[5] The presence of a continuous blood supply within the choriocapillaris of rabbits likely contributed to a higher heat capacitance against thermal damage than ex vivo testing.[5,17] Lastly, the continuous movement of the beam spot over the adhesive also prevented localized heating beyond the retinal damage threshold. The absence of visible and histological retinal changes while using the adhesive technology is likely due to a combination of these factors.

The results from this study confirmed that the laser parameters used to activate the adhesive for repairing penetrating corneal incisions[1,4] did not result in any noticeable ophthalmoscopic or histologic retinal damage. With the previously known higher safety margins of this laser in humans, compared to pigmented rabbits, the use of this adhesive to repair penetrating corneal incisions is not likely to cause retinal changes in humans. The use of this laser is not without risk, particularly at higher powers, and utmost care is still required for limiting exposure to patients and clinicians during its operation. Non-human primate models or a pilot human trial could further assess in vivo tolerability, corneal healing, and laser retinal safety as future work.

The strengths of this study included the use of a pigmented rabbit eye model possessing a shorter anterior-posterior diameter that translates to higher safety margins in the larger human eye. The in vivo nature also permitted observation of delayed retinal changes, and healing after laser exposure, that could suggest initial photochemical changes developing into histologic changes with time. The use of untreated areas of the retina as internal controls also reduced the number of animals required for this study. A limita-tion of this study was that it did not assess for poten-tial retinal damage from accidental laser overlap at the peripheral margins of the adhesive. This could be assessed in future studies by applying the laser without the adhesive. This study was also not designed to assess for the type or severity of photochemical changes and relied solely on ophthalmoscopic and histologic appearance for retinal changes after laser exposure.

Conclusion

The laser parameters required to activate an adhesive designed to seal penetrating corneal incisions, did not result in any ophthalmoscopically or histologi-cally visible retinal lesions immediately after exposure, and after 168 hours in the pigmented Dutch Belted in vivo rabbit model. Based on this, it is unlikely to cause retinal changes in humans. This laser can cause retinal damage to all layers of the neural retina, including the RPE, when it was operated stationarily at higher power.

Acknowledgments

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