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Analysis of a method for establishing a model with more stable chronic glaucoma in rhesus monkeys

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ABSTRACT

In this study, we utilized yellow-wavelength laser treatment and measured aqueous outflow facility to establish a model for chronic glaucoma in rhesus monkeys. We then compared the effects of photocoagulation resulting from exposure to the yellow laser or to a green laser. Twelve rhesus monkeys were used to establish the model, and the yellow and green lasers were utilized for 360° photocoagulation in the anterior-chamber angles of the right eye in all subjects. After certain periods of time before and after the creation of the glaucoma model, the cornea, aqueous humor, optic cup, intraocular pressure (IOP), outflow facility, retinal nerve fiber layer (RNFL), and pathology of the trabecular meshwork were analyzed. Both the yellow and green lasers caused an increase in IOP compared with before photocoagulation (18.6 ± 2.6 mm Hg and 16.1 ± 1.8 mm Hg, respectively), with an average photocoagulation from the yellow and green lasers of 39.2 ± 7.9 mm Hg and 30.3 ± 4.7 mm Hg, respectively ($P < 0.01$). However, the success rate of a second photocoagulation treatment in the yellow laser group was significantly higher than in the green laser group ($P < 0.05$). After the increase in IOP, both groups exhibited an inflammatory response in the anterior segment, enlarged cupping, and a decrease in the average thickness of the RNFL. However, the yellow laser caused less corneal edema than the green laser ($P < 0.05$), and the outflow facility of the two groups (0.33 ± 0.09 and 0.30 ± 0.07 μl/min/mm Hg for the yellow and green lasers, respectively) showed different degrees of differences (0.05 ± 0.02 and 0.07 ± 0.02 μl/min/mm Hg for the yellow and green lasers, respectively) into the abnormal range after photocoagulation. Pathological examination revealed that the depth of destruction of the trabecular meshwork appeared to be deeper in the yellow laser group than in the green laser group. In conclusion, application of a yellow laser combined with measuring aqueous outflow facility produced a glaucoma model with a minor inflammatory response and few IOP fluctuations.

1. Introduction

Glaucoma is a group of pathological conditions often involving increased intraocular pressure (IOP), which threatens and irreversibly damages the visual function of the optic nerve (Quigley, 1999). Nearly 30% of glaucoma patients progress to blindness without effective treatment (Quigley and Broman, 2006). The current studies on the pathogenesis and treatment of glaucoma have received widespread attention, but research has been limited due to the lack of an established stable model of glaucoma. The current animal models for chronic glaucoma include rats, mice, rabbits and monkeys (Bouhenni et al., 2012; Dautriche et al., 2014). Compared with rodents, the close phylogeny and high homology between monkeys and humans makes monkeys an excellent model for studying glaucoma (Bouhenni et al., 2012). Common methods used to create a rhesus monkey model of glaucoma have included laser photocoagulation of the trabecular meshwork (Pederson and Gaasterland, 1984) and anterior-chamber injection of latex particles (Weber and Zelenak, 2001), but the former is the more widely used method (Ollivier et al., 2004). Although argon lasers (Sasaoka et al., 2008; Lam et al., 2009; Dai et al., 2012) and green lasers (Nork et al., 2010; Albrecht May et al., 2006) have commonly been used to

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create glaucoma models in rhesus monkeys, the possibility of severe postoperative inflammation as well as excessive photocoagulation and other associated complications persist. Early lasers utilized argon ions as an excitation substance and are classified as gas lasers that generate a single-wavelength (green). With continuous development, dye lasers were created, and the most commonly used have been solid neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers and diode lasers, which can create green-, yellow-, and red-wavelength instruments, all of which are primarily used for the treatment of retinal diseases. We established a rhesus monkey model of chronic glaucoma using a yellow-wavelength laser. Due to its relatively long wavelength and its biological characteristics, which differ from those of green lasers, the role and response of target tissue were different in experiments utilizing the yellow laser, thereby establishing a more stable chronic glaucoma model with mild inflammation. Currently, there have been no reports of a rhesus monkey model of chronic glaucoma involving a specific yellow-wavelength laser.

2. Materials and methods

2.1. Ethics statement

This study strictly adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and was approved and monitored by the Institutional Animal Care and Use Committee of Zhongshan Ophthalmic Center.

2.2. Subjects and procedures

Twelve healthy adult rhesus monkeys (4 females and 8 males; Blue Island Biological Technology Co., Ltd., of Guangdong, Guangzhou, China, Qualification), with initial body weights of 7–12 kg and initial ages of 4–6 years, were used in this study. Before creating the models, the animals underwent various tests to confirm the overall health of their eyes, including slit-lamp microscopy (Topcon, SL-D7, Japan) and photography (Topcon, DC-3, Japan), gonioscopic examination (VOLK, G-1 Trabeculum, USA), fundus photography (TRC-50DX Retinal Camera; Topcon, Tokyo, Japan), optical coherence tomography (OCT; Stratus OCT, Carl Zeiss Meditec, Dublin, CA, USA), Tono-Pen XL tonometry (Reichert, Depew, NY < USA), and Schiotz tonography (YZ7A Tonometer, 66 Visiontech Co., Ltd., China). The cornea, aqueous humor, anterior-chamber angle, IOP, cupping and retinal nerve fiber layer (RNFL) were observed by the above-mentioned examinations after photocoagulation. Measurement of IOP was performed weekly between 9:00 AM and 12:00 PM using a Tono-Pen XL tonometer. Each eye was measured 3 times, and the values were averaged. The subject's pupil was enlarged before measuring the RNFL by OCT biweekly. The aqueous outflow facility was measured in the supine position during application of a recording Schiotz tonometer with a standard 5.5-g weight over a period of 4 min every two weeks (particularly when elevated IOP returned to normal) before and after photocoagulation to assess the effects of photocoagulation in the trabecular meshwork on outflow facility.

2.3. Anesthesia

All procedures were performed under anesthesia with an intramuscular injection of ketamine hydrochloride (10–20 mg/kg, Ketalar 50®, GuTian Pharmaceuticals Ltd, Fujian, China) plus chlorpromazine hydrochloride (3.5 mg/kg, Ketalar 50®, GuTian Pharmaceuticals Ltd, Fujian, China). Topical proparacaine HCl (Alcaine®, 0.5%, Alcon Laboratories, Ft. Worth, TX) was used for all procedures involving contact with the cornea.

2.4. Establishment of the model

Laser-dedicated gonioscopy (Volk, G-1 Trabeculum, USA), multi-wavelength solid-state lasers and associated multiplier slit-lamp microscopes (VISULAS Trion & LSL Trion Laser Slit Lamp, Carl Zeiss Meditec AG, Goeschwitzer Strasse, Jena, Germany) were used to perform 360° photocoagulation in the functional trabecular meshwork area (meshwork area, which lays behind two-thirds of the trabecular meshwork) of the right eye in all subjects. Photocoagulation was continuous with adjacent spots and with paleness or small air bubbles in the trabecular meshwork, which is standard for the selected laser energy (Fig. 1B). After the laser treatment, subjects without an elevated IOP did not receive treatments for the following two weeks. Those with an increased IOP that returned to

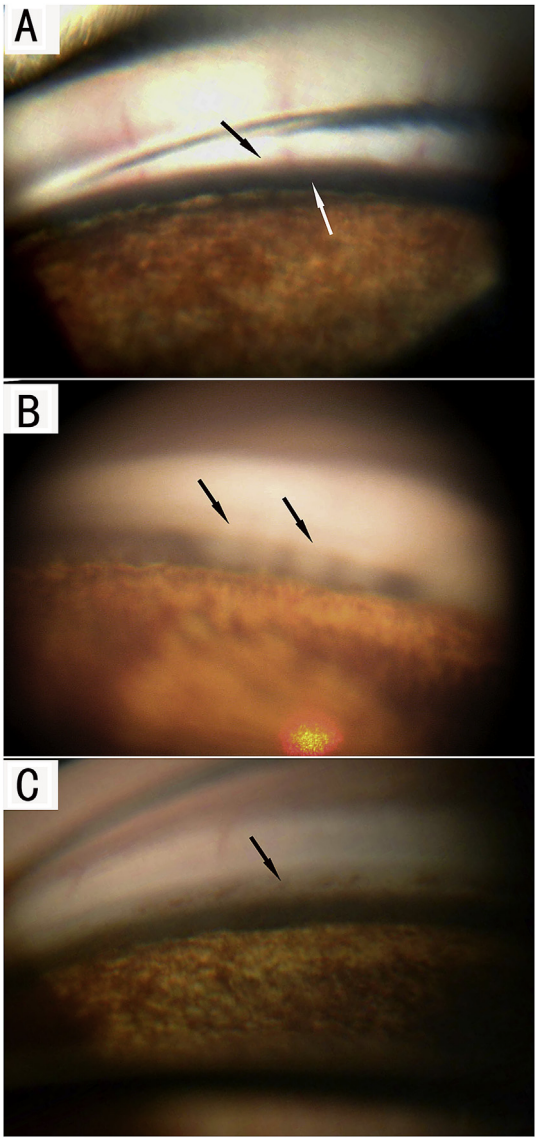

Fig. 1. Gonioscopic images of the anterior-chamber angle before and after photocoagulation. A shows the pre-treatment appearance of the anterior-chamber angle and wide-angle display. The ciliary body band is brown and wide (white arrow), and there is a light-pigmentation trabecular meshwork (black arrow). B shows anterior-chamber angle changes with photocoagulation, showing whitening of the trabecular meshwork and surrounding tissues (black arrows). C shows the outside of the anterior-chamber angle after photocoagulation at the fourth week, with light pigmentation on the surface of the trabecular meshwork (black arrows).