• Basic Research •

Experimental circumferential canaloplasty with a new Schlemm canal microcatheter

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Abstract

• AIM: To present a new, simple, inexpensive Schlemm canal microcatheter for circumferential canaloplasty in a rabbit model.

• METHODS: A rabbit glaucoma animal model was established by intravitreal injection of triamcinolone acetonide. Circumferential canaloplasty with a new Schlemm canal microcatheter (patent license number: 201220029850.0) was performed. The Schlemm canal microcatheter was composed of microcatheter wall and lumen. The wall was made of high refractive index plastic optical fiber that could be attached to an illuminant so that the whole lighted microcatheter was visible during circumferential canaloplasty. The lumen could be attached to an injector for injection of viscoelastic during catheterization. Rabbits were divided randomly into the control, model and treatment groups. Intraocular pressure (IOP) was measured with a Tono-pen tonometer pre-operation and 3, 7, 14, 21 and 28d post-operation. Ultrasound biomicroscopy was performed to visualize the Schlemm canal microcatheter in the Schlemm canal and the sclera pool.

• RESULTS: The Schlemm canal microcatheter could be used to perform circumferential canaloplasty in the rabbit glaucoma animal model. IOP was lower in the treatment group than that in the model group 3, 7, 14 and 28d after operation. There were no significant differences in IOP between the control group and treatment group. The differences among the three groups were statistically significant (3d: *F*=41.985, *P*<0.001; 7d: *F*=65.696, *P*<0.001; 14d: *F*=114.599, *P*<0.001; 28d: *F*=55.006, *P*<0.001).

• CONCLUSION: Circumferential canaloplasty is safe and effective in control of experimental glaucoma model in rabbits.

• KEYWORDS: glaucoma; canaloplasty; Schlemm canal; microcatheter; surgery

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INTRODUCTION

Glaucoma is the second leading cause of blindness and the leading cause of irreversible blindness worldwide. The number of people with glaucoma worldwide is estimated to be 76.0 million in 2020 and 111.8 million in 2040[1]. The classic surgical treatment for glaucoma is trabeculectomy. Glaucoma shunt, Fugo blade and glaucoma drainage valve are new surgical techniques for the treatment of open angle glaucoma. Trabeculectomy, glaucoma shunt, Fugo blade and glaucoma drainage valve are all glaucoma drainage surgeries that create a bypass route for aqueous humor to drain out of the eye and into a subconjunctival bleb. However, glaucoma drainage surgeries presents many intraoperative and postoperative complications, such as hypotony, shallow anterior chamber, choroidal hyperemia, decompression retinopathy and macular edema, as well as bleb-related problems such as bleb infection, endophthalmitis and ocular discomfort. Many scholars have attempted to restore or increase the effusion of physiological aqueous humor outflow, to eliminate bleb-related complications and avoid anti-metabolic drug related complications[2-6].

Canaloplasty is one of clinical pearls from clinical trials in glaucoma[7-8]. Canaloplasty is a minimally invasive and maximally effective treatment for glaucoma[3]. Canaloplasty does not create a permanent fistula in the wall of the eye and does not require a bleb. Therefore canaloplasty is a 'bleb-free' surgery and avoids bleb-related complications. Multi-center clinical trials confirmed that canaloplasty could significantly reduce the intraocular pressure (IOP) of open angle glaucoma patients and canaloplasty had less intraoperative and postoperative complications[7,9-14]. Canaloplasty enhances the physiological aqueous humor outflow by the circumferential

viscodilation the Schlemm canal with a microcatheter (iTrack™, Ellex iScience, Inc., Fremont, CA, USA)[9-10]. The iTrack™ has a complex structure and it is expensive. In this report, we presented a new, simple, inexpensive Schlemm canal microcatheter (patent license number: 201220029850.0). The Schlemm canal microcatheter is made of high refractive index plastic optical fiber. The microcatheter can circumferentially viscodilate the Schlemm canal. We studied the efficacy of the Schlemm canal microcatheter in a rabbit glaucoma animal model.

MATERIALS AND METHODS

Rabbit Glaucoma Animal Model Healthy male gray rabbits with clear ocular media (weight 5±0.5 kg, Experimental Animal Center of Fujian Medical University, China.) were used in this study. This study was performed in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (Permit Number: 2014-YK-103). Rabbits were weighed and anesthetized with pentobarbital sodium (20 mg/mL/kg, P3761, Sigma-Aldrich, St. Louis, MO, USA). Local anesthesia was achieved with oxybuprocaine (Benoxil®, Santen, Japan).

The rabbit glaucoma animal model has been previously reported[15-16]. Briefly, the eye was sterilized with 5% povidoneiodine (Shanghai Likang Disinfectant Hi-Tech Co., Ltd., China), for 1min before the intravitreal injection. After washing with physiological saline, the eyes in the model group and the treatment group were administrated an intravitreal injection of 4 mg/0.05 mL triamcinolone acetonide (Tianjin Kingyork Group Co. Ltd., China), 2.5 mm behind the limbus using a 30-gauge needle. The eyes in the control group were administrated an intravitreal injection of 0.05 mL physiological saline. After injection, the injection site was pressed with a cotton swab for 30s to prevent backflow. The contralateral eye was left untreated. Eyes were given ofloxacin ophthalmic solution (Tarivid®, Santen, Japan) three times per day after modeling. IOP was measured with a Tono-pen tonometer (Reichert, Inc., Depew, New York, USA) in the morning (10 a.m. to 11 a.m.) pre-injection and 3d post-injection. IOP was measured three times for each eye, and the mean IOP was recorded. The rabbits with hypertension (IOP >21 mm Hg) were included as glaucoma animal model.

Structure of the Schlemm Canal Microcatheter Structure of the Schlemm canal microcatheter was shown in Figure 1.

Surgical Procedure of Circumferential Canaloplasty with Schlemm Canal Microcatheter Four days after establishing glaucoma animal model, rabbits in the treatment group were submitted to circumferential canaloplasty with the Schlemm canal microcatheter. The procedure has been previously reported[17-19]. Briefly, the procedure for circumferential canaloplasty was shown in Figure 2. A conjunctival flap with fornix conjunctiva as the basement was created. Two nonpenetrating scleral flaps were created to expose the Schlemm canal. The superficial scleral flap was approximately 50% thick and the deep scleral flap was removed. The two

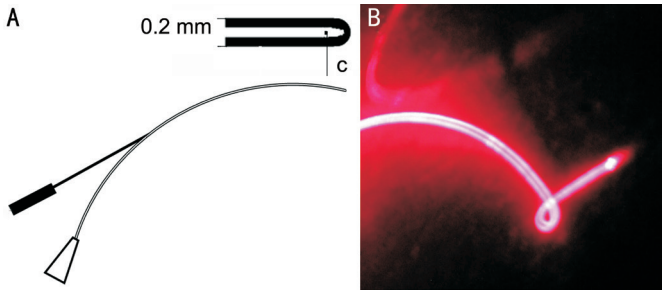

Figure 1 Structure of the Schlemm canal microcatheter (patent license number: 201220029850.0) A: The Schlemm canal microcatheter was composed of microcatheter wall and lumen. The wall was made of high refractive index plastic optical fiber that could be attached to an illuminant so that the whole lighted microcatheter was visible during circumferential canaloplasty. The lumen could be attached to an injector for the injection of viscoelastic during catheterization; B: The whole Schlemm canal microcatheter was lighted when attached to the illuminant.

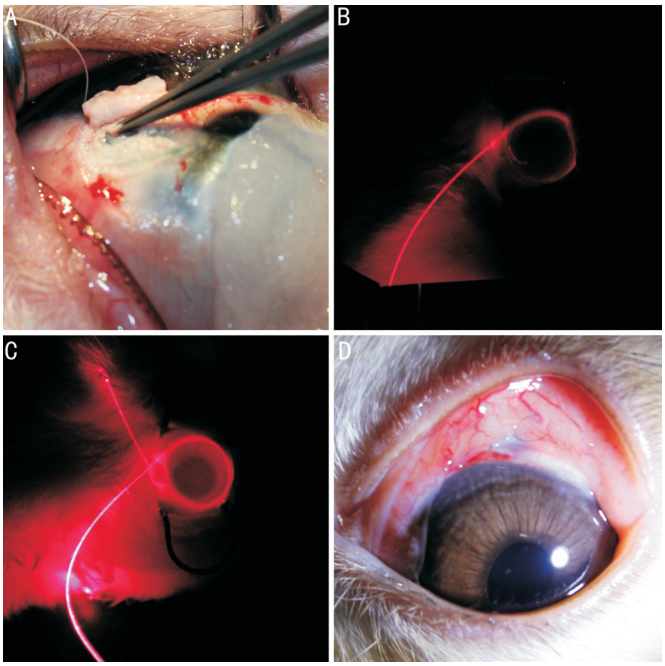

Figure 2 Circumferential canaloplasty procedure A: Two nonpenetrating scleral flaps were created to expose the Schlemm canal. The deep scleral flap was removed; B: Next the Schlemm canal microcatheter was inserted into the Schlemm canal. The lighted microcatheter enabled us to visualize the microcatheter while 180 degree circumferential canaloplasty; C: The lighted microcatheter enabled us to visualize the microcatheter while 360 degree circumferential canaloplasty. Circumferential canaloplasty was performed until the microcatheter emerged at the other end of the canal ostia; D: The superficial scleral flap and the conjunctival flap were repositioned and sutured to ensure a watertight closure.

ostias of the Schlemm canal were dilated with healon. Next the Schlemm canal microcatheter was inserted into the Schlemm canal. The lighted microcatheter enabled us to visualize the microcatheter while circumferential canaloplasty. The lumen of the microcatheter allowed us to inject healon every two clock hours as the microcatheter was pushed forward. Circumferential canaloplasty was performed until the microcatheter emerged at the other end of the canal ostia. The microcatheter was retracted. The superficial scleral flap and the conjunctival flap were repositioned and sutured to ensure a watertight closure. Eyes were administered an ofloxacin ophthalmic solution (Tarivid®, Santen, Japan) three times per day after modeling. Ultrasound biomicroscopy (UBM) was performed to visualize the Schlemm canal microcatheter in the Schlemm canal and the sclera pool.

Grouping and Treatment Rabbits were acclimated for 1wk and divided randomly into the control, the model and treatment groups. Each group contained 6 rabbits. The rabbit glaucoma animal model was established in the model and treatment groups. Rabbits in the treatment group were administrated circumferential canaloplasty. Rabbits in the control and model groups were administrated sham operation. IOP was measured with a Tono-pen tonometer in the morning (10 a.m. to 11 a.m.) pre-operation and at 3, 7, 14, 21 and 28d postoperation.

Statistical Analysis The data were presented as mean±SD. The data were analyzed using an ANOVA analysis with a LSD *t*-test for multiple comparisons, with $P<0.05$ being considered to be statistically significant.

RESULTS

The Schlemm canal microcatheter in the Schlemm canal and the sclera pool was shown with UBM in Figure 3. UBM showed that the Schlemm canal was dilated. There were two arcs of strong echo, which indicated that the Schlemm canal microcatheter was in the Schlemm canal. A scleral lake under the superficial scleral flap. The trabecular meshwork inside the scleral lake was continuous. This finding indicated that the operation was a non penetrating glaucoma filtering surgery.

There were no significant differences in IOP among three groups pre-modeling ($F=0.068$, $P=0.934$). After modeling, IOP of the model group and the treatment group was higher than that in the control group. The differences among three groups were statistically significant ($F=69.729$, $P<0.001$). There were no significant differences in IOP between the model group and the treatment group. At 3, 7, 14 and 28d after surgery, IOP in the treatment group was lower than that in the model group. There were no significant differences in IOP between the control group and the treatment group. The differences among the three groups were statistically significant (3d: $F=41.985$, $P<0.001$; 7d: $F=65.696$, $P<0.001$; 14d: $F=114.599$, $P<0.001$; 28d: $F=55.006$, $P<0.001$) (Table 1).

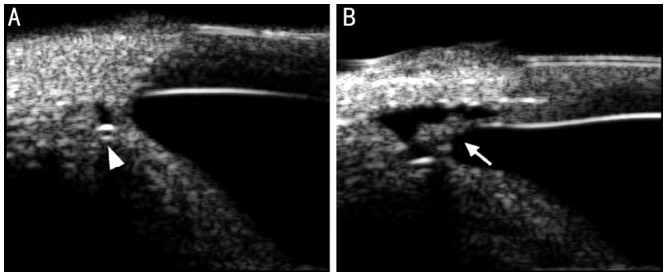

Figure 3 UBM showed the Schlemm canal microcatheter in the Schlemm canal and the sclera pool A: UBM showed that the Schlemm canal was dilated and the Schlemm canal microcatheter was in the Schlemm canal (white triangle); B: UBM showed a scleral lake under the superficial scleral flap. The trabecular meshwork inside the scleral lake was continuous (white arrow).

Table 1 Preoperative and postoperative mean IOP among the three groups ($n=6$)

Parameters	Control group	Model group	Treatment group
Pre-modeling	14.2±2.1	14.3±2.8	14.7±2.2
Pre-operation	14.5±2.1	32.8±3.8[a]	32.0±3.0[a]
3d post-operation	14.2±1.9	32.2±4.3[a]	16.3±4.4[b]
7d post-operation	14.7±2.0	31.5±3.4[a]	15.7±3.0[b]
14d post-operation	14.2±2.1	32.8±2.5[a]	15.5±2.5[b]
28d post-operation	14.7±2.7	31.8±4.0[a]	16.8±2.3[b]

[a]$P<0.05$ *vs* control group; [b]$P<0.05$ *vs* model group.

DISCUSSION

In this study, we observed that IOP in the treatment group decreased after circumferential canaloplasty in a rabbit glaucoma model. This finding was consistent with the results of clinical studies. Lewis *et al*[11] reported a three years result that the mean IOP in all study eyes decreased from a baseline IOP of 23.8±5.0 mm Hg to 15.2±3.5 mm Hg. The mean number of glaucoma medications used decreased from 1.8±0.9 to 0.8±0.9. Bull *et al*[20] reported a three years result that the mean IOP in all study eyes decreased from a baseline IOP of 23.0±4.3 mm Hg to 15.1±3.1 mm Hg. The mean number of glaucoma medications used decreased from 1.9±0.7 to 0.9±0.9. These demonstrated that canaloplasty could cause a significant and sustained decrease in IOP for patients with open angle glaucoma. Circumferential canaloplasty is a safe and effective anti-glaucoma surgery.

In this study, we performed circumferential canaloplasty with a new Schlemm canal microcatheter. At present, circumferential canaloplasty requires the use of iTrack™. iTrack™ is composed of an optical fiber, lumen, catheter support wire and polymer shaft and distal atraumatic tip. The optical fiber can be attached to iLumin™ so that the lighted tip was visible during circumferential canaloplasty. The lumen can be attached to ViscoInjector™ for injection of viscoelastic during catheterization. The iTrack™ components include glass, metal and polymer shaft. The structure of iTrack™ is complex

and difficult to make. Furthermore iTrack™ is expensive. We designed a new, simple, inexpensive Schlemm canal microcatheter (patent license number: 201220029850.0). The Schlemm canal microcatheter is composed of microcatheter wall and lumen. The wall is made of high refractive index plastic optical fiber that can be attached to an illuminant so that the whole lighted microcatheter was visible during circumferential canaloplasty. The lumen can be attached to an injector for injection of viscoelastic during catheterization. The whole Schlemm canal microcatheter is lighted when attached to an illuminant. The flexibility and folding properties of the microcatheter are superior to those of the glass fiber. Even if the Schlemm canal microcatheter was folded into a very small circle, it does not crack. Our previous study found that the iTrack might break when it was folded to a diameter less than 10 mm, while the microcatheter would not break even when it was folded to 5 mm. Therefore, we do not worry about the microcatheter may be cracked and damage when the microcatheter is clamped too strongly. The component of the Schlemm canal microcatheter, the plastic optical fiber is simple and cheap. The structure of the Schlemm canal microcatheter is simple and easy to make. Thus, the Schlemm canal microcatheter will be cheaper than iTrack™.

The mechanism of circumferential canaloplasty is to catheterize and viscodilate all the aqueous humor outflow resistance, including the trabecular meshwork, Schlemm canal and collector channels. In this study, we employed a rabbit glucocorticosteroid induced glaucoma model. The mechanism of glucocorticosteroid induced glaucoma may be associated with a loss of trabecular meshwork cells, thickening of trabecular beams and a increased deposition of extracellular matrix material in the aqueous humor outflow pathway, particularly in the juxtacanalicular tissue and the endothelium of the Schlemm canal inner wall[15-16,21]. The clinical features, morphology and molecular mechanisms of glucocorticosteroid induced glaucoma are similar to those of primary open angle glaucoma. Therefore, the glucocorticosteroid induced glaucoma animal model is an attractive animal model which to study the specific aspects of primary open angle glaucoma[15-16,21]. In this study, we made several improvements to the animal model.

First, the concentration of the intravitreal injection of triamcinolone acetonide was 4 mg/0.05 mL. Previous studies reported that the concentration of triamcinolone acetonide was 4 mg/0.1 mL. A 0.1 mL of injection volume will easily lead to acute high IOP after injection. This volume may cause retinal vein occlusion and retinal artery occlusion. The pathogenesis of acute high IOP is not the same as that of open angle glaucoma. Acute high IOP easily causes injection reflux, resulting in individual differences in the drug dose. Second, adult rabbits were selected for modeling. We found that modeling with young rabbit easily leads to corneal dilatation, Descemet's membrane rupture, corneal opacity and other complications. These manifestations are similar to infant glaucoma. Third, gray rabbits are selected for modeling. There are a lot of pigment particles in gray rabbit's trabecular meshwork and ciliary body. Pigment particles help to clearly distinguish the trabecular meshwork and ciliary bodies, which is helpful in determining whether the Schlemm canal microcatheter is in the Schlemm canal.

Circumferential canaloplasty is a minimally invasive and maximally effective glaucoma treatment[9]. Without a subconjunctival bleb, circumferential canaloplasty has fewer complications and patients feel more comfortable. There are few possible complications of the Schlemm canal microcatheter. The most common complications were microhyphema or hyphema. The hyphema was absorbed by the 1-week follow-up visit. Rare complications included trabecular meshwork scar and Descemet's membrane detachments. We recommended injecting healon every two clock hours as the microcatheter was pushed forward. If there was resistance when the microcatheter was pushed forward, the microcatheter was retracted a slightly, injected with healon and then pushed forward. We observed that the microcatheter was stable. However, if the microcatheter will be used in human studies, medical device biological evaluations including tests for stability, *in vitro* cytotoxicity, genotoxicity, carcinogenicity, reproductive toxicity, local effects after implantation, irritation and delayed type hypersensitivity are required. In summary, we presented a new, simple, inexpensive Schlemm canal microcatheter for circumferential canaloplasty.

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