

Progression on canaloplasty for primary open angle glaucoma

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Abstract

• **As a non-penetrating glaucoma surgery (NPGS), canaloplasty aims to reconstruct the physiological outflow of aqueous humor by dilating the Schlemm's canal. Ab interno canaloplasty (ABiC), which can reconstruct the natural outflow pathways of aqueous humor in mild-to-moderate primary open angle glaucoma (POAG) patients, is a new minimally invasive glaucoma surgery (MIGS) procedure improving from traditional canaloplasty. Canaloplasty can reduce intraocular pressure (IOP) with high efficiency and security. There are no complications such as scar formation and encapsulation for this no-bleb canaloplasty.**

• **KEYWORDS:** glaucoma; canaloplasty; ab-interno canaloplasty

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INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide^[1]. It is estimated to be 3.54% of the the global prevalence of glaucoma. The number of people with glaucoma worldwide (aged 40-80y) will increase to 111.8 million in 2040^[2]. Currently intraocular pressure (IOP) reduction is the only therapeutic measure for glaucoma management. The effective treatment for glaucoma not only is reduction of IOP but also is modulation of IOP^[3]. In medically uncontrolled primary open angle glaucoma (POAG), the gold standard for reduction of IOP is trabeculectomy^[4]. However, serious complications, such as bleb encapsulation, bleb scarring, wound leakage, shallow anterior chamber, hypotension and choroidal detachment are associated with trabeculectomy.

Canaloplasty is a newly developed surgery by circumferential viscodilation and tensioning of Schlemm's canal with a flexible microcatheter^[5]. It reconstructs and increases the natural outflow of aqueous humor. This minimally invasive glaucoma surgery (MIGS) which has better clinical application prospects^[6] can avoid the complications of the traditional incisional glaucoma surgery.

ORIGIN OF CANALOPLASTY

As a non-penetrating glaucoma surgery (NPGS), canaloplasty aims to reconstruct the physiological outflow of aqueous humor by dilating the Schlemm's canal^[7]. The flexible microcatheter (Menlo Park, California, USA) guided by He-Ne laser was inserted and leaded in the Schlemm's canal to a circle. A single or double 10-0 prolene suture was tied to the distal tip. The microcatheter was withdrawn and leaded back through the canal in the opposite direction. A 30G needle was used to inject Healon GV into the canal at every two clock hours while the catheter was withdrawn. The suture was retained in the Schlemm's canal to reduce the outflow resistance and increase the permeability of the trabecular meshwork (TM), Schlemm's canal and juxtacanalicular portion. The outflow of aqueous humor was increased through the tensioned canal and the IOP was reduced. Grieshaber *et al*^[8] compared the results of two different types of sutures in canaloplasty. It was found that the 10-0 suture group had lower IOP and higher success rate than 6-0 suture group.

THE MECHANISM OF CANALOPLASTY IN PRIMARY OPEN ANGLE GLAUCOMA SURGERY

Xin *et al*^[9] reported that the mechanisms of IOP reduction in reconstruction of aqueous outflow drainage (RAOD) in POAG of canaloplasty were as follows: 1) Circumferential dilation of the Schlemm's canal (SC) and surrounding collector channels. Swain *et al*^[10] reported that Schlemm's canal collapsed in most POAG patients. The Schlemm's canal was expanded and the aqueous humor outflow was increased during the reconstruction of the physiological aqueous humor outflow system. At the same time, the partitions, bridge and valve-like structures in the Schlemm's canal were cut off. 2) Instant formation of microcracks through RAOD procedures. Irshad *et al*^[11] reported that the average diameter of Schlemm's canal *in vivo* was 121 micron, while the microcatheter was 250 micron. This would make the Schlemm's canal expand

sufficiently during the process of microcatheter insertion and viscodilation. The endothelial cells and TM of the Schlemm's canal were broken slightly simultaneously. The micropore of the Schlemm's canal can be directly connected with the surrounding tissue. 3) Formation of more pores, and local detachment between the Schlemm's canal endothelium (SCE) and basement membrane. The resistance of the inner wall of Schlemm's canal restricts aqueous humor outflow. Braakman *et al*^[12] reported that the number of pores on Schlemm's canal wall was reduced in glaucoma patients. More pores of the Schlemm's canal were made by biomechanical tension. The outflow of aqueous humor was increased with the tight junction among endothelial cells, basement membrane and surrounding tissues. 4) Activation of stem cells by constant mechanical stress caused by the tensional suture placed at the anterior part of the Schlemm's canal. Braunger *et al*^[13] reported that there were a group of typical cells near the Schwalbe line confirmed by immunohistochemical staining. TM stem cells could differentiate into TM cells with phagocytic function by constant mechanical stress in glaucoma patients. Roubex *et al*^[14] reported that IOP decreased rapidly and persistently when bone marrow mesenchymal stem cells were injected into the eyes of mice with ocular hypertension. The expression of COT4 and Sox2 markers were up-regulated with the persistence of TM tension. Then TM stem cells differentiate and migrate to repair the glaucomatous damaged TM and the aqueous humor outflow was increased^[15]. 5) Reversal of TM herniation. TM was attached to the outer wall of Schlemm's canal under the physiological IOP. However, the TM entered Schlemm's canal to form TM hernia under high IOP. Canaloplasty could relieve TM hernia and dilate Schlemm's canal^[16]. 6) Mobilization of the reserve of the aqueous drainage. Chang *et al*^[17] reported the segmental outflow of aqueous humor was determined by the uneven distribution of pores and collecting channels in Schlemm's canals. The collecting channels modulated the IOP when it fluctuates. This imbalanced segmental outflow was more prominent in glaucoma patients. 7) Change of SCE phenotype. The endothelium of Schlemm's canal possess the characteristic of lymphocytes and vascular endothelium. The integrity of Schlemm's canal were determined by lymphocyte regulatory factors PROX1 and vascular endothelial growth factor-C/-3. Lymphocytes possess the characteristic of drainage. The IOP of some incisional filtration surgery with failed bleb was well controlled, which may be related to the stimulated lymphocyte configuration cells. These cells could restore and reconstruct the physiological drainage function of Schlemm's canal. 8) Strengthened mechanical induction and conduction of TM: Fuchshofer and Tamm^[18] reported that the degenerated TM would cause the increase of resistance of aqueous humor outflow. The hardness of the aqueous humor outflow system

was depended on TM and extracellular matrix. Changes in tissue hardness could also lead to changes in TM^[19]. Continuous biomechanical tension by suture in canaloplasty could stimulate the cellular regulation of TM and extracellular matrix. It could also activate stem cells to secrete cytokines. These molecules and cytokines could adjust and repair the dysfunctional microenvironment of TM.

COMPARISONS BETWEEN CANALOPLASTY AND OTHER TYPES OF GLAUCOMA SURGERY FOR POAG

Compared with trabeculectomy, canaloplasty has the following advantages: 1) no filtering bleb formation; 2) without antimetabolites; 3) rapid visual recovery; 4) fewer complications; 5) simple postoperative nursing; 6) stable postoperative IOP. Khaimi^[20] reported that canaloplasty was as effective as trabeculectomy. Compared to trabeculectomy complications, many of these problems were easily resolved and some should perhaps not be classified as complications at all. As noted earlier, a study by Grieshaber^[21] showed that the absence of microhyphaema on the first postoperative day actually seems to be a negative prognostic indicator in uneventful canaloplasty procedures in patients with POAG. It is reported that the success rates of trabeculectomy were 80%, 66.2% and 42% in 2, 3 and 4y respectively, while canaloplasty was 76%, 52.9% and 21% respectively^[22]. Harvey and Khaimi^[23] reported that canaloplasty had repeatedly been shown to be safe and effective at significantly lowering IOP and medication dependence in different patient populations with POAG. Whites, blacks and selected Asian patients responded similarly to canaloplasty making this procedure favorable for many races despite the more robust scar tissue formation seen in blacks or the narrower angle anatomy seen in Asians. Interventions of failed filtering blebs include needling, subconjunctival injection of 5-FU and other complicated post-operative nursing. Most postoperative patients of trabeculectomy have the ocular surface problem. Heidelberg corneal scan revealed conjunctival microcysts formation and dilatation of aqueous veins which suggested that canaloplasty could increase aqueous humor passing through sclera and conjunctiva. It was also the mechanism of IOP reduction in canaloplasty^[24].

The integrity and function of Schlemm's canal could be assessed by blood reflux which could be observed by gonioscopy examination or Schlemm's canal fluorescence angiography. Congestion and emptying of Schlemm's canal were slower in mild-to-moderate glaucoma and there was almost no blood filling in advanced glaucoma. When IOP was below 30 mm Hg, the distribution of blood reflux was consistent; when IOP was between 30-40 mm Hg, blood reflux was dotted and patchy; when IOP was above 50 mm Hg, there was almost no blood reflux. Poor blood filling in

Schlemm's canal indicated the poor outcome of canaloplasty. Gandolfi *et al*^[25] and Rekas *et al*^[26] reported a prospective randomized controlled study of the safety and efficacy of canaloplasty and non-penetrating deep sclerectomy. Totally 29 eyes underwent canaloplasty and 30 eyes underwent deep sclerectomy. IOP in the canaloplasty group decreased from 19.0±6.9 to 12.6±2.7 mm Hg, and in the non-penetrating deep sclerectomy group decreased from 19.1±5.8 to 14.3±3.5 mm Hg ($P<0.05$). There was no significant difference in IOP and dosage of glaucoma drugs between the two groups before and 12mo after operation respectively ($P>0.05$). The success rates of the two groups were 79.0% and 76.9% ($P=0.701$). Anterior chamber hyphema (58.0%) was the most common complication in canaloplasty group. Filtering bleb fibrosis (26.7%) was the most common complication in the non-penetrating deep sclerectomy group. The patients in canaloplasty group did not need special nursing postoperatively. But in deep sclerectomy group, 58.7% needed postoperative intervention including 5-FU subconjunctival injection, scleral suture removal or dialysis and filtering bleb needling.

ADVERSE EVENTS AND COMPLICATIONS ASSOCIATED WITH CANALOPLASTY

When compared with trabeculectomy, canaloplasty offers a more favorable side effects profile^[23]. Inability to cannulate Schlemm's canal, Descemet's membrane detachment and improper microcatheter passage are the main side effects of canaloplasty. Postoperative microhyphaema is a positive prognostic indicator in canaloplasty^[27]. The outflow of blood from the collector channels indicated that the channels of aqueous humor outflow was opened and effective. There were 1.9% patients with TM damaged by suture and 26% patients unfinished with tension suture placed in the canaloplasty. There were 11% postoperative choroidal detachment, 9.8% hypotension and 9.1% Descemet's membrane detachment. There were 1.6% IOP higher than 30 mm Hg postoperatively related to Schlemm's canal collapsed and the collector channels' opening closed. The tension of sutures in canaloplasty varies with each individual. Loose suture could not reduce the drainage resistance and IOP. Tight suture could increase the drainage resistance of aqueous humor by narrowing the TM gap^[7].

CANALOPLASTY COMBINED WITH OTHER OPERATIONS AND DRAINAGE IMPLANTATION IN POAG

In POAG, canaloplasty combined with phacoemulsification can reduce IOP more significantly than single operation^[28]. Stegmann Schlemm canal dilator was a new implantable device that would make canaloplasty a simple, controllable and reproducible procedure. The material of the expander was polyimide resin, biocompatible, and non-metallic. The device has a diameter of 240 microns that was used to expand TM and

Schlemm's canal permanently. Grieshaber *et al*^[29] reported that 45 patients with POAG of white race who were treated with medication for uncontrolled IOP (IOP was still >21 mm Hg at the maximum dose of two or more antiglaucoma medications and in the middle stage, with optic cup enlargement and corresponding visual field defect in advanced glaucoma) underwent canaloplasty combined with Stegmann Schlemm canal dilator. It showed that 98% of the patients had IOP less than 21 mm Hg, 88% less than 18 mm Hg, 86% less than 16 mm Hg and no anti-glaucoma drugs were used in all patients in two-year follow-up.

EVOLUTION, ADVANTAGES AND DISADVANTAGES OF INTERNAL CANALOPLASTY FOR POAG

Ab interno canaloplasty (ABiC) is a new type of minimally invasive surgery for glaucoma^[30]. The incision is about 1.5-1.8 mm wide through the temporal transparent cornea. After injecting viscoelastic agent into the anterior chamber, the microcatheter is inserted into the anterior chamber. The TM and the inner wall of Schlemm's canal are cut horizontally with gonioscope. The incision is about 1 mm wide and the tip of iTrack is inserted into Schlemm's canal. The TM tissue herniated in the Schlemm's canal is separated by injecting viscoelastic agent every two o'clock while withdrawing the microcatheter. ABiC remove the hernia of TM in Schlemm's canal and collector channels by expanding Schlemm's canal entirely. ABiC has completely restored the aqueous humor drainage system as traditional canaloplasty. ABiC could restore complete conjunctival and scleral tissue with no permanent implants. ABiC has the following advantages: 1) Restoring of aqueous humor drainage system with safe and effective IOP reduction for mild-to-moderate POAG. 2) Small incision, quick healing and less nursing postoperatively. 3) An option for glaucoma patients without permanent implants. 4) No filtering bleb formation and no bleb-related complications. ABiC does not affect the further incisional glaucoma surgery. The disadvantage of ABiC are: 1) The target IOP may not reached to low teen for advanced glaucoma. 2) Primary angle-closure glaucoma (PACG) and secondary glaucoma related to iritis, neovascular glaucoma, angle-recession glaucoma are not the indications for ABiC. 3) Expensive surgical equipment and long learning curve.

FUTURE APPLICATION OF CANALOPLASTY IN GENE THERAPY FOR POAG

The method of reducing permanent outflow resistance through gene therapy has attracted extensive attention of researchers. But the safety and effectiveness of TM-targeted gene therapy needed to be further developed. Canaloplasty can be used for direct delivery of gene vectors in Schlemm's canal and TM for gene therapy of POAG. Tian and Kaufman^[31] reported that Schlemm's canal and the cells of the inner wall of the

juxtacanalicular tissue were the target of gene therapy. Gene therapy by canaloplasty could transfer nucleic acid vector to the target tissue and improve its expression which can reduce the resistance of aqueous humor outflow. Gene therapy can permanently reduce the outflow resistance of aqueous humor with the development of molecular biology and gene technology. At present, TM targeting gene therapy includes dominant inhibition of Rho gene, Rho kinase, exoenzyme C3 transferase, calmodulin binding protein and so on^[32]. Gene therapy for POAG can induce immune inflammation in anterior chamber by injecting gene carrier material through corneal incision. Thus, gene vector is loaded into Schlemm's canal by canaloplasty. Virus vectors from Schlemm's canal to TM increases substantially for Schlemm's canal to break slightly when injected the viscoelastic agent. Additionally, the transgene expression at the TM/Schlemm's canal is further enhanced by expression of the whole Schlemm's canal. No immune inflammation was induced in anterior chamber by canaloplasty gene therapy for POAG.

PROSPECT

POAG is a major public health problem with its increasing prevalence and substantial impact on quality of life for patients, their families, and caregivers. MIGS procedures could reduce IOP with lower risk than traditional filtration surgery. Canaloplasty is an option for mild-to-moderate POAG and antimetabolites are not needed. There is no filtering bleb formation and less surgical induced astigmatism (SIA) in this minimally invasive operation^[33]. For its safety and effectiveness, canaloplasty will change the current concept of POAG. Canaloplasty focus on reconstruct of the aqueous humor physiological drainage directly. Continuous stretching of sutures in Schlemm's canal promotes and strengthens the drainage of aqueous humor. Future research should focus on how to simplify the operation procedure. ABiC is the most minimally invasive canaloplasty at present. It can reduce the economic burden of glaucoma medications, avoid the complications of traditional glaucoma filtration surgery and lessen the complex postoperative care. Canaloplasty will play an important role in POAG treatment.

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