MODERN TECHNOLOGIES OF OPEN-ANGLE GLAUCOMA SURGERY

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© **S.N. Svetozarskiy,** Clinical Resident, the Department of Eye Diseases;
Y.A. Maslennikova, Postgraduate, the Department of Eye Diseases;
M.V. Anikeeva, Head of the Laboratory, the Department of Eye Diseases

Nizhny Novgorod State Medical Academy, Minin and Pozharsky Square, 10/1, Nizhny Novgorod, Russian Federation, 603005

Currently, glaucoma surgery has become a major technique. Surgery is a method of choice in open-angle glaucoma, especially in those cases when conservative and laser treatments have no effect, as well as if glaucoma is inaccessible or a patient has low treatment compliance. In this review the authors give the information about the development of main glaucoma surgery directions, such as removal of pupillary block, the anterior chamber fistulization, the reduction of intraocular fluid production. Drainage surgery, its history and modern technical devices have been characterized in detail. The design of drainage devices has been improved towards their size reduction, extension of filtration area and the development of valve mechanisms. Indications for their implementation in open-angle glaucoma treatment, and the factors contributing to a successful treatment have been discussed. There have described early and late complications of microdrainage and paid particular attention to obliteration of developed outflow pathways, being the main problem as they reduce the effect of filtering and draining operations. The authors have presented a number of advanced micro-invasive technologies, both used in clinical practice (Ex-PRESS™ mini-shunt, Trabectome™, iStent, canaloplasty and viscocanalostomy), and those being under clinical study — SOLX Gold Micro-Shunt, CyPass, Hydrus™ Microstent a canalicular scaffold, AqueSys Microfistula Implant. There has been presented the information on design and technology of these devices with their detailed classification based on the differences in their mechanism of action, operative approach type and material used.

Key words: open-angle glaucoma; glaucoma treatment modality; glaucoma surgery.

In accordance with current concepts, glaucoma is a group of diseases characterized by increased intraocular pressure (IOP), which is higher than tolerance limit, accompanied by optic neuropathy and typical decrease of visual functions. Glaucoma management primarily aims at maintaining visual organ function. Glaucoma therapy is based on the disease monitoring in order to prevent progressive glaucoma optic neuropathy, stabilization of visual functions by maintaining target IOP. IOP decrease by every 1 mm Hg reduces glaucoma progression risk by 10% [1], and pressure reduction should be stable, since tunneling of vision relates more to pressure variation and, statistically, to standard error, rather than to IOP arithmetic mean [2, 3]. And IOP fluctuations induced by various factors can reach high values [4].

Currently, glaucoma surgery has become a major technique, and in some cases it is a method of choice, even if glaucoma is newly diagnosed. The experience of Nizhny Novgorod Regional Ophthalmological Clinic (Russia) shows that more than half the patients who sought medical advice for glaucoma in 2012 required surgical management. There are various approaches to determine surgical indications for glaucoma patients. According to meta-analysis carried out by J. Burr et al., there are no significant differences between visual field variation degree within five years in groups of patients who primarily underwent conservative or surgical treatment [5]. Surgery is a method of choice in open angle glaucoma, if conservative and laser treatment has no effect, as well as in case of inaccessibility or low patient's compliance. The last-mentioned should be paid particular attention to taking into consideration the represented data on greater significance of IOP fluctuation rather than IOP mean value [6].

Background. In 1856 Albrecht von Graefe (1828–1870) for the first time performed iridectomy in acute glaucoma attack, and shortly after that de Wecker performed the first sclerectomy (1858), in Russia the first fistulizing operation — oblique sclerectomy sclerotomy — was carried out by A.N. Maklakov (1887). Subsequently, cyclodialysis (1900) and thermocauterization (1932) were suggested. Thus, by the early 1930s there were formed such basic glaucoma operative approaches as papillary block removal, anterior chamber fistulization, intraocular fluid production decrease [7]. Trabeculectomy was developed in experiment by H.S. Sugar (1961), and introduced in clinical practice by J.E. Cairns (1968). Subsequently, antimetabolites — 5-fluorouracil and Mitomycin-C were used in glaucoma surgery. Deep scleroctomy was suggested by S.N. Fedorov (1974), non-penetrating sclerectomy — by V.I. Kozlov et al. (1987), sinustrabeculectomy and sinusotomy — by M.M. Krasnov et al [8–10]. However, insufficient efficacy of the proposed techniques, a great number of

For contacts: Svetozarskiy Sergey Nicolaevich, +7 950-622-76-75; e-mail: svetozarskij@rambler.ru

refractory glaucoma patients characterized by persistent increased IOP, resistant to medical and surgical intervention have caused the search and development of new techniques and devices for glaucoma surgical management.

Complications of micro-draining surgeries

IOP characteristic	Early complications	Late complications
Increased	Shunt (valve) malfunction Occlusion (by ligature, fibrin, blood clots, iridial or vitreous entrapment) Misdirected aqueous humur outflow Suprachoroidal hemorrhage Choroidal effusion Tube retraction	Incapsulation Subconjunctival fibrosis Fibrosis in the area of internal opening
Hypotony	Hyperfiltration Humor leakage through conjunctiva wound Eyeball perforation Choroid detachment	Shunt extrusion

Drainage devices. Drainage surgery developed in incremental steps [11]. Setons (Lat. *seta* — bristle) draining aqueous humor along the proper surface as outflow drainage (silk thread, artery wall, polymer materials, etc) was first used as early as in 1866 by Wecker (a gold wire). Later, there were brought forward shunt-tubes draining anterior chamber humor in a filtering subconjunctival bleb. Further, shunt construction was complicated, drainage devices were developed, in which a distal end of a shunt-tube was connected to polymer case (body) of a drain tube fixed posteriorly from (scleral sulcus) limbus. Drainage devices were elaborated towards size reduction, filtration area increase and development of valve mechanisms.

Currently, among drainage devices, the most relevant ones in clinical practice are nonvalved drainage devices Molteno (Molteno Ophthalmic Ltd., New Zealand) and Baerveldt (Advanced Medical Optics, Inc., USA), and valve models Krupin (Eagle Vision, Inc., USA) and Ahmed (New World Medical, Inc., USA) [12, 13]. Their application enables to have an effect similar to that of conventional surgeries, however, there is no convincing evidence confirming the advantage of a particular device [14]. The main indication for drainage device usage is refractory glaucoma, which includes such clinical forms as a failed operated primary glaucoma, neovascular glaucoma, uveal glaucoma, pigmentary glaucoma, juvenile glaucoma, closed-angle "creeping" glaucoma, etc, but today micro-shunting is widely used also in patients with primary open-angle glaucoma at the first stage of surgical treatment [15].

Ahmed implant due to its valve mechanism is characterized by the higher safety level in relation to postoperative hypotony. A valve mechanism has a cone-shaped chamber due to Venturi effect, valve opening pressure being 8.0 mm Hg. By its clinical efficiency the device is as good as Mitomycin-C-based trabeculectomy [16]. In particular, its efficiency in refractory glaucoma 1 or 5 years after the surgery (IOP maintenance in the range from 5 to 21 mm Hg, with or without medicinal drugs) is 80 and 49% respectively [17]. However, year by year after implantation, the number of working devices of any type decreases, first of all, due to incapsulation, and 5 years later the number averages 50% [12, 16, 17].

Obliteration of developed outflow pathways is a major problem eventually reducing the effect of all filtering and draining operations using both common and novel devices. Doctor D.Y. Yu et al. [18] was the first who focused ophthalmologists' attention on the fact that correct formation of outflow pathway is of great importance as well as device construction. Operative technique should primarily provide minimum conjunctiva damage, and, secondarily, prepare outflow pathway to its lymph net. W. Schmidt et al. [19] thinks the solution is in the differentiated pharmacological accompanying of surgeries, in particular, in the selection of anti-metabolites depending on proliferation properties and differentiation of fibroblast subtypes forming corresponding eye structures.

However, drainage micro-surgery has its drawbacks, both in operative technique, and in design and size of devices, biocompatibility of materials [20] that in some cases result in early and late complications related mainly to failure of developed outflow pathways (See the Table). Moreover, if draining devices are placed improperly there can develop corneal edema, keratitis, cataract.

New-generation micro-invasive technologies. In the late XX century new-generation micro-invasive technologies for glaucoma management were developed. Among them there are the following devices and surgical treatment modalities [17, 21, 22]:

1) Ex-PRESS™ mini-shunt (Alcon, USA);
2) Trabectome™ (NeoMedix, Inc., USA);
3) iStent (Glaukos Corporation, USA);
4) Canaloplasty (iScience Interventional, USA);
5) SOLX Gold Micro-Shunt (SOLX, Inc., USA);
6) CyPass (Transcend Medical, USA);
7) Hydrus™ Microstent a canalicular scaffold (Ivantis Inc., USA);
8) AqueSys Microfistula Implant (AqueSys, Inc., USA).

New techniques differ in the mechanism of hypotensive effect, material of devices, as well as in operative technologies. Exposure of anterior chamber angle structures by conjunctival and scleral flap dissection has been called external approach — ab externo, and penetration into anterior chamber through corneal incision (like in phacoemulsification) — internal approach, ab interno.

It should be noted, that not all the mentioned techniques are used in practice. Food and Drug Administration (FDA), USA, has not yet approved SOLX Gold Micro-Shunt, CyPass, Hydrus™ Microstent, AqueSys Microfistula Implant. Trabecular micro-stent iStent combined with cataract surgery in 2012 was recommended for application.

Ex-PRESS™ (Excessive Pressure Regulation Shunt System) mini-shunt was suggested in 1998 (M. Belkin, Y. Glovinsky), made in Israel (Optonol Ltd., since 2010 — Alcon). A shunt is made of medical steel, it is a tube, 2.64 mm in length, outside diameter being 400 μm (27 G) and inside diameter — 50 μm. The device has a spur-like projection for fixation in anterior chamber, plate on base, and extra anti-lock opening situated on a semi-axis so that if a shunt is placed in anterior chamber, it will face cornea. Drainage device is implanted in anterior chamber under scleral flap through an opening in scleral sulcus area (ab externo) followed by scleral flap and conjunctiva suturing. Implantation characteristics have been described by a number of foreign and Russian researchers [23, 24], the description of shunt explantation technique and re-implantation in case of intraoperative error was novel [25, 26]. There has been presented shunt implantation technique through sclera tunnel without conjunctiva dissection [27]. The technique complies with the abovementioned requirements for minimal conjunctiva damage.

Minimally invasive implantation, a low level of intra- and postoperative complications, capability to lead to a sustained IOP decrease enable to compare mini-shunt efficiency with that of trabeculectomy [28, 29]. A prospective, randomized study [30] involving 15 patients with open-angle glaucoma of both eyes appeared to be the most descriptive and significant. All the patients underwent trabeculectomy on one eye, and implantation — on a fellow eye. A two-year follow-up showed these surgeries to be little different in postoperative IOP, while Ex-PRESS™ implantation less frequently causes complications (20 versus 33%) and the necessity of postoperative surgeries (0 versus 27%), as well as requires the administration of the fewer IOP-lowering agents. Mini-shunt implantation does not result in changes of anterior segment parameters (angle size, depth, volume) within three follow-up months [31]. As for the material (stainless steel) biocompatibility is concerned, animal experiments using Mitomycin-C showed no significant differences in tissue structure in the formation of filtering bleb and capsule around Ex-PRESS™ mini-shunt and a silicon drainage tube [32]. Histological examination (post mortem and after enucleation) of patients operated on for glaucoma with mini-shunt implantation revealed good biocompatibility of the device, formation of a thin fibrous cap, and no inflammatory cells 24 months after the surgery [33, 34]. Considerable experience of this glaucoma therapy technique application in Russia and abroad gives various authors the reason to recommend mini-shunt implantation as a primary surgery in case there are medical indications for glaucoma therapy [15], or as trabeculectomy alternative in a group of patients with target IOP 13–15 mm Hg [23]. A mini-shunt is proved to maintain its position and have no effect on MRI quality, 1.5 and 3.0 T, but comes into motion if magnetic field density is 4.7 T [35, 36]. We consider that a metal shunt located in the anterior segment is prone to tissue cutting. Moreover, any metal device even made of medical steel when placed in reactive media is exposed to an oxidative process.

Ab interno trabeculectomy performed using Trabectome™, and iStent implantation are referred to ab interno surgeries on Schlemm's canal and gonioscopy-assisted [37]. The procedures aim at overcoming the resistance of trabecular apparatus in open-angle glaucoma and prepare aqueous outflow pathway from anterior segment to Schlemm's canal avoiding a trabecular net. Ab interno trabeculectomy includes focal ablation and cauterization of a trabecular net over a period from 90 to 120° using Trabectome™, which has a tip — a microelectrocauter [38]. When a micro-stent is placed, direct connection between the anterior segment and Schlemm's canal is formed. iStent micro-stent is made of medical titanium, it is a heparin-covered, right-angled tube, 1 mm in length, outside diameter being 250 μm and inside diameter — 120 μm. The anterior segment via corneal short-scar incision at 3 o'clock is filled by viscoelastic, a applicator with a stent is placed and put through anterior chamber till scleral spur and iris root are reached in lower nasal quadrant, the stent is placed in Schlemm canal lumen by its pointed end, while the second end remains turned towards anterior segment [39].

Canaloplasty (iScience) and viscocanalostomy are referred to ab externo operations on Schlemm`s canal and combined with filtration surgery [40, 41]. In viscocanalostomy, viscoelastic is injected in Schlemm's canal in order to broaden canal lumen and form mini-ruptures in its inner wall. In canaloplasty, viscoelastic is injected in Schlemm`s canal through an incision similar to that in trabeculectomy, then a flexible probe with a light emitting diode at the end (iScience, diameter of different types vary from 250 to 400 μm) is inserted full-length in the canal lumen [42]. Polypropylene thread 10-0 is inserted into Schlemm`s canal lumen with the help of a probe, the ends of the thread being tied with tension that provides Schlemm`s canal lumen retention in a long-term postoperative period and more significant, compared to viscocanalostomy, IOP decrease [43]. Other surgeries are used in both open-angle and narrow-angle glaucomas including those performed as one-stage operations with phacoemulsification. The necessary condition of effectiveness is the integrity of the distal part of outflow — collecting canaliculi, episcleral recepient veins; it can be determined by blood reflux provocation in gonioscopy or

according to fluorescent canalography. The absence of artificial openings and filtering bleb on eyeball surface, as well as aqueous outflow control determined by physiological resistance of classic outflow pathway should result in complication risk reduction, particularly, hypotony. Indeed, ab interno trabeculectomy and canaloplasty less frequently cause side effects [44–46].

SOLX Gold Micro-Shunt is a gold plate, 3.2x5.2 mm in size, with numerous micro-channels. A shunt is implanted in suprachoroidal space ab externo, where aqueous humor is drained via channels from the anterior chamber under pressure gradient [47].

Micro-shunt CyPass is a perforated tube made of polyamide material (thermoresistant biocompatible polymer), 6.35 mm in length, inside diameter being 0.3 mm, outside — 0.51 mm, at one end there is plate and three retaining rings. Viscoelastic fills the anterior chamber through 1.5 mm corneal dissection, then cyclodialysis is performed using a blunt end of a stent mounted on delivery system. After that a micro-stent is pushed in suprachoroidal space (ab interno). The ring fix the stent in sclera spur area and iris root, plate is left faced towards the anterior chamber. First results of micro-stent application showed its efficiency and safety in open-angle glaucoma management [48].

Hydrus™ Microstent is a tube frame made of nitinol, 8 mm in length, implanted ab interno in Sclemm's canal lumen. Nitinol is shape memory material, titanium NiTi nickelide, which is not alloy but intermetallide — a compound with fixed atomic ratio. The name of the material is an acronym consisting of the first letters of the components' elements and the place of its discovery — Naval Ordnance Laboratory, USA (Nickel Titanium Naval Ordnance Laboratory). Currently, Hydrus™ Microstent efficiency is being studied within the framework of international clinical trials "Hydrus IV" (phacoemulsification combined with micro-stent implantation has been performed since February 2012) and experimental studies [49].

AqueSys Microfistula Implant, as well as its new version — XEN Gel Stent, is a gelatin (hydrolyzed collagen) tube. The device is implanted ab interno in suprachoroidal space using injecting device similarly used in phacoemulsification. Gelatin drainage changes pattern in tissues. Now phase 3 of clinical trials is being carried out (2012–2014).

Based on the most essential characteristics of the techniques described, we suggest the following classification of modern surgical techniques for glaucoma management using drainage devices.

I. By mechanism of action:

1. Draining of anterior chamber humor into episcleral reservoire: drainage devices Molteno, Baerveldt, Krupin, Ahmed Glaucoma Valve.

2. Formation of a new outflow pathway through a filtering bleb under scleral or conjunctival flap: Ex-PRESS™ mini-shunt.

3. Formation of a new outflow pathway into suprachoroidal space — intrascleral systems: AqueSys Microfistula Implant, CyPass, Gold Micro-Shunt.

4. Forcing of aqueous outflow in Sclemm`s canal: ab interno trabeculectomy, iStent, Hydrus™ Microstent, canaloplasty (iScience).

II. By operative approach type:

1. External approach (ab externo): canaloplasty (iScience), Gold Micro-Shunt, Ex-PRESS™.

2. Internal approach (ab interno): AqueSys Microfistula Implant, CyPass, iStent, Hydrus™ Microstent.

III. By the material of implantable devices:

1. Metals and alloys: Ex-PRESS™, SOLX Gold Micro-Shunt, Hydrus™ Microstent, iStent.

2. Polymer materials: canaloplasty (iScience), CyPass.

3. Biomolecules: AqueSys Microfistula Implant.

As the experts from evidence-based healthcare center (John Hopkins University, USA) note, now it is impossible yet to conclude about the efficacy of a particular technique for glaucoma management, since researchers are not provided enough information on the changes of optic nerve and visual field in patients under study [50, 51]. Not all the existing techniques can be compared with the gold standard of conventional surgery in terms of hypotensive effect and the rate of complications [52, 53]. New randomized studies are required to prove clinical efficiency of novel technologies compared with conventional ones concerning IOP reduction, as well as steady stabilization of visual functions, the latter being the main goal of glaucoma treatment.

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