Early bleb needling revision after glaucoma filtering surgery


Petrov S. Yu.


Antonov A. A.


Vostrukhin S. V.


Panyushkina L. A.


Safonova D. M.

Scientific Research Institute of Eye Diseases of the Russian Academy of Medical Sciences, 11 A,B, Rossolimo St., 119021, Moscow, Russian Federation

SUMMARY

Clinical case of early-onset cystic filtering bleb following trabeculectomy with sinusotomy is presented. Patient complained of a discomfort in an eye in 4 weeks after the surgery. The prescribed eye drop regimen was followed irregularly. Thin, high, limited, and hyperemic cystic bleb was visualized on slit lamp examination. IOP was 27 mm Hg without any medical therapy. Anti-inflammatory (tobramycin/dexamethasone fixed combination) and glaucoma (brimonidine/timolol fixed combination) therapy was prescribed. In a day, needling of filtering bleb with its wall destruction and subconjunctival injections of dexamethasone, fluorouracil, and ranibizumab was performed (IOP was 20 mm Hg). The next day, filtering bleb flattened, hyperemia decreased, numerous conjunctival microcysts were visualized in the central zone. IOP reduced to 10.2 mm Hg. No choroidal effusion was identified by ophthalmoscopy and OCT. The patient continued to receive anti-inflammatory treatment. In two weeks, preventive needling with the same drugs was performed due to some increase of hyperemia. At the end of follow-up (week 4), filtering bleb was flat and diffuse, IOP was 13.2 mm Hg. Dexamethasone instillations (1 or 2 times a day) were prescribed for a month.

This case study describes a technique of functioning filtering bleb repair with its wall destruction and anti-inflammatory, cytostatic, and anti-VEGF agents injections to prolong the effect of glaucoma filtering surgery under excessive scarring.

Keywords: trabeculectomy, filtering bleb, Wurzburg bleb classification score, dexamethasone, fluorouracil, VEGF inhibitors, needling revision.

Financial disclosure: Authors has no financial or property interests related to this article.

The authors declare that there are no conflicts of interest.

Ophthalmology in Russia. — 2014. — Vol. 11, No 3. — P. 80–88

«No matter how perfectly a surgical filtering procedure is carried out, it can be jeopardized by inappropriate maneuvers or prescriptions during follow-up» — Peng Khaw [1].

Dr. Khaw is one of the top European specialists in glaucoma surgery and co-author of the Moorfields Safe Surgery System that represents an integrated approach to trabeculectomy. This system has gained a great popularity in Europe.

Indeed, postoperative management (topical agents as well as active manipulations with filtering bleb) prolongs the effect of glaucoma filtration surgery.

Topical steroids (usually as a fixed-dose combination with topical antimicrobial), topical non-steroid anti-inflammatory drugs and topical cycloplegic agents (useful in choroidal detachment) or glaucoma drops (to prevent postop IOP spikes due to reduced outflow of aqueous humor through the novel pathway) are essential components of perioperative care. Currently, the following drugs are used in ophthalmology.

Dexamethasone is a synthetic corticosteroid with anti-inflammatory, desensitizing, and immunosuppressive effects. It suppresses inflammation by inhibiting the release of inflammatory mediators, reducing the number of mast cells, decreasing vascular permeability, and stabilizing cellular membranes. The drug affects all stages of the inflammation, i.e., it inhibits the synthesis of prostaglandins from arachidonic acid and the production of pro-inflammatory cytokines. Dexamethasone drops are prescribed 4 times a day for different periods depending on indications.

Non-steroid anti-inflammatory drugs (NSAIDs) decrease the activity of cyclooxygenase, an enzyme that is re-

Contact information: Petrov Sergey Yur'evich post@glaucomajournal.ru

sponsible for prostaglandin synthesis. Ophthalmic NSAIDs reduce inflammation and pain by inhibiting the generation and transmission of pain impulses along nerve fibers. In early post-op period, NSAIDs are prescribed 4 times a day.

When prescribing anti-inflammatory therapy, a surgeon anticipates maximum prolongation of hypotensive effect due to the prevention of postoperative scarring in filtering bleb area. However, according to many investigators, absolute efficacy of modern glaucoma filtering surgery varies greatly.

Active early postoperative management including subconjunctival injections of cytostatic and anti-VEGF agents into the bleb site, suture removal (they can be lasered or cut, or pulled out), and mechanical revision of bleb walls and subscleral space in the course of needling, is a characteristic tendency of current ophthalmology.

When analyzing recent data on the efficacy of glaucoma surgery, one can speculate about a novel principle of its assessment by counting the number of the above-mentioned procedures required to control IOP. Therefore, at the end of follow-up mean IOP is similar in all study groups but the efforts applied to achieve this result differ. This is the key principle of glaucoma surgery assessment.

Let us describe briefly the above-mentioned techniques and pharmacological agents.

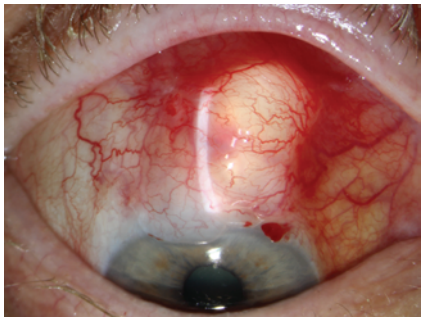

Fig. 1. Cystic, thin-wall, high, limited, and hyperemic filtering bleb (hyperemia 26%, true IOP 27 mm Hg), day 1.

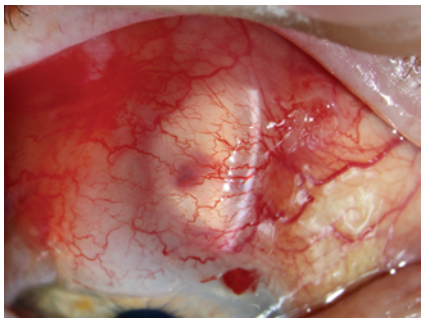

Fig. 2. Filtering bleb after 2 days of topical treatment (no changes in hyperemia and true IOP).

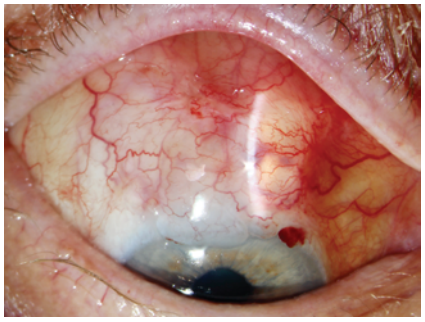

Fig 3. Filtering bleb on the next day after needling revision (hyperemia 14%, true IOP 10.2 mm Hg).

Bleb needling revision is performed with 27-gauge or 30-gauge needle. This procedure that re-establishes aqueous humor outflow through the novel surgical pathway is included in the Standards of specialized medical care in glaucoma.

Bleb needling can be performed in the early or late period following the original glaucoma surgery. Early needling (within the first weeks post-op) with cytostatic and anti-inflammatory agents prevents significant scarring. Late needling mechanically breaks up fibrotic tissue that limits bleb surface area. There are two types of bleb needling revision, i.e., subconjunctival (sub-Tenon's) needling and subscleral flap needling.

Cytostatic agents, fluorouracil (FU) and mitomycin C (MMC), are commonly used in clinical practice as well.

Mitomycin is an anti-cancer drug isolated from Streptomyces caespitosus that finds its use in complex chemotherapy. This off-label agent is not approved for ophthalmology. It prevents excessive scarring following glaucoma surgery due to the inhibition of the whole cycle of fibroblast proliferation and collagen synthesis. MMC is given intraoperatively.

Fluorouracil (FU) is an anti-cancer antimetabolite drug. Its indications for use are similar to MMC. In ophthalmology, FU is used off-label as well. FU is considered to be 100-300 times less potent and, therefore, less toxic than MMC. Subconjunctival injections of FU are given postoperatively. The single dose does not exceed 5 mg. The total dose may be up to 105 mg. However, dose-dependent complications limit the treatment course with 10 injections even in high risk of scarring [2, 3].

It is well-known that different isoforms of vascular endothelial growth factor (VEGF) play a role in inflammatory and reparative processes, e.g., VEGF165 stimulates angiogenesis, VEGF189 promotes fibroblast production, and VEGF121 provides both effects. In addition, VEGFs increase vascular permeability [4-9] thus resulting in plasma protein leakage and extravasal fibrin gelation [10]. Finally, thick scar fibrotic tissue with vessels forms in the surgical site.

Two anti-VEGF agents are commonly used in ophthalmology, mainly for the treatment of wet age-related macular degeneration (AMD), i.e., ranibizumab/Lucentis and bevacizumab/Avastin. Ranibizumab is approved for ophthalmology while bevacizumab is used off-label. According to many studies, bevacizumab efficacy is similar to ranibizumab, however, bevacizumab is much less expensive than ranibizumab.

These drugs can be used postoperatively following glaucoma surgery due to their potent anti-inflammatory activity. Currently, dozens of studies on bevacizumab injections into the bleb site were published [11-13].

According to many data, postoperative injections of VEGF inhibitors into outflow pathways prolong hypotensive effect [14-15].

The doses of anti-VEGF agents for the injection into the bleb site and for intravitreal administration are similar.

The recommended dose of bevacizumab (concentrate for solution for infusion, 100 mg/4 ml) is 0.05 ml/1.25 mg.

A number of investigators compared hypotensive efficacy of VEGF inhibitors by different routes of administration, i.e., intravitreal and intracameral injection, injection into the bleb site (the latter two are preferred since they ensure targeted drug delivery to the site of potential scarring), and subconjunctival injection (the most simple route). Maximum plasma concentration of the drug was detected following intravitreal administration. Hypothetically, this is correlated with systemic side effects [16].

The dosages of cytostatic agents are of great importance due to their high cytotoxicity. According to the published data, bleb needling revision is usually performed with a solution that contains 5 mg of FU (5%). However, many surgeons initially inject FU with an insulin 30-gauge needle peripherally to the bleb and then approach and puncture the bleb with a 25-gauge needle. This technique minimizes the risk of drug entry into anterior chamber. Additionally, aqueous humor filtering from the bleb washes out the drug from the site of its target administration. We utilize another strategy and initially perform bleb needling revision and then inject the drug thus providing its maximum concentration in the filtering area. In addition, about 0.4 ml of solution is accumulated in subconjunctival space near the dissected bleb. This prevents IOP fluctuations which are possible when needling revision is performed under ocular hypertension. When performing re-needling, we use half as many concentration of FU. Trypan blue for capsular staining (0.08%) helps to visualize fluid distribution [2]. Trypan blue staining demonstrated that the drug occasionally penetrates into anterior chamber. Nevertheless, this concentration is safe and induces no early or late-onset corneal endothelium damage.

Mitomycin-augmented bleb needling revision is performed much less frequently than FU-augmented procedure, however, the experience with FU using is positive. 0.1 ml (0.04 mg/ml) of the drug is injected subconjunctivally with a 30-gauge needle which enters the conjunctiva approximately 5 to 10 mm from the bleb site. Following the injection, bleb needling revision is performed [17].

Most authors prefer to dilute cytostatic agents with saline or water for injections and to prescribe steroid drops every hour for the first 2 weeks. In Russia, such steroid dosage regimen is uncommon since their use is considered to provoke complications associated with cytostatic drugs, i.e., wound leakage and corneal epithelium decompensation. Therefore, direct dexamethasone injection into the bleb site regards as a more effective and safe steroid therapy.

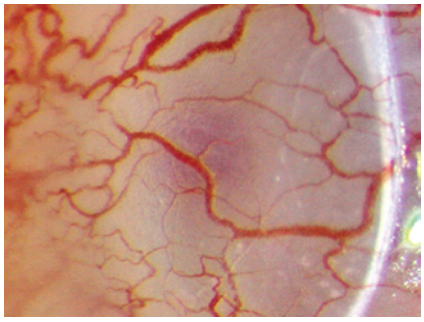

Fig 4. Conjunctival microcysts at the bleb site. Microcysts appear as tissue irregularities in thin semitransparent conjunctiva above the accumulation of aqueous humor.

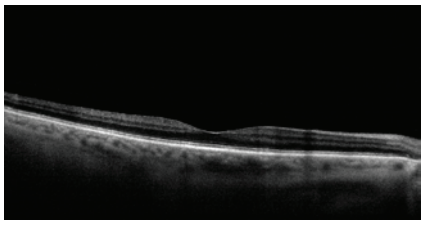

Fig. 5. OCT, the next day after needling revision (RTVue-100, Optovue, Fremont, CA).

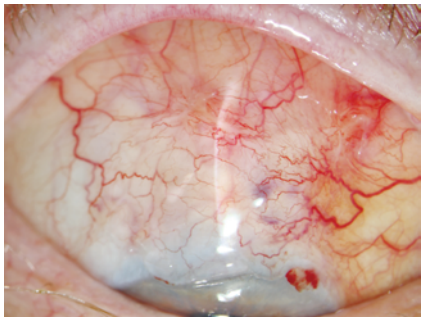

Fig 6. Filtering bleb, final exam in 4 weeks (hyperemia 8%, true IOP 13.2 mm Hg).

According to some data, FU and bevacizumab could be added into a syringe with dexamethasone (up to a total volume of 0.4 ml). This complex treatment is highly effective, however, their compatibility is unknown. Additionally, subconjunctival administration of these drugs is off-label.

Regardless of a variety of excessive scarring prevention measures, patient adherence (or compliance) is an important issue since «drugs don't work in patients who don't take them» (EGS Guidelines, 4th edition).

Here, we present a clinical case of bleb needling revision performed in a month after the initial glaucoma filtering surgery in a patient who failed to follow the prescribed treatment.

CLINICAL CASE

81-year-old man presented with severe ocular discomfort in 4 weeks following sinus trabeculectomy with basal iridectomy for uncontrolled primary open-angle glaucoma. There were no associated ocular diseases (excepting immature cataract) nor eye surgery. The patient found difficulties in specifying the prescribed topical medications since he did not use them regularly.

Day 1. Primary exam, therapy prescribing

Cystic, thin-wall, high, limited, hyperemic filtering bleb which provoked ocular discomfort was seen under the slit lamp (see Fig 1). According to the Wurzburg bleb classification score (WSCS) that evaluates bleb vascularity, corkscrew vessels, encapsulation, and microcysts, the total bleb score was 1 point (blebs with a WBCS of ≥8 points are associated with a good prognosis) [18].

Conjunctival vessels were dilated and tortuous and have a corkscrew-like appearance. The degree of conjunctival redness which was evaluated using «Hyperemia-3» software (average redness intensity was calculated as the percentage of the red channel of RGB image) was 26% [19]. At this term, conjunctival hyperemia normally averages about a 10-13%.

IOP measured by pneumotonometry was 27 mm Hg. No glaucoma drops were used.

According to F. Grehn, these clinical findings are the indication for active topical anti-inflammatory therapy and bleb needling revision with cytostatic agent and VEGF inhibitor. However, needling revision under the ocular hypertension could be accompanied by subconjunctival fluid leakage and anterior chamber flattening. This results in ciliochoroidal effusion which complicates further activation of aqueous humor outflow. In these instances, pre-treatment with topical beta blockers and topical carbonic anhydrase inhibitors is prescribed. The lack of hypotensive effect requires oral carbonic anhydrase inhibitors (acetazolamide).

The patient was prescribed with a fixed-dose combination of timolol and brinzolamide (Azarga® eye drops) and anti-inflammatory topical drugs (Tobradex® and Nevanac® 3 times a day).

Day 3. Exam, needling revision

Two days later, no visible improvements were observed, however, IOP decreased from 20 to 27 mm Hg (see Fig. 2).

Considering that IOP was fairly controlled, bleb needling revision with its lateral wall dissection and subconjunctival injection of dexamethasone, FU, and ranibizumab near to the bleb site was performed. The procedure was accompanied by subconjunctival fluid leakage and anterior chamber flattening. To avoid further complications, cycloplegic agent (Cyclomed®) 2 times a day was prescribed. Anti-inflammatory treatment was proceeded whereas hypotensive therapy was discontinued.

Day 4. Exam, therapy correction

The day after the needling revision the bleb was more flat and diffuse and less hyperemic. WBCS was 7 points, conjunctival redness decreased from 26% to 14% (see Fig. 3). Anterior chamber depth was of normal value, true IOP was 10.2 mm Hg.

Slit lamp examination revealed multiple solid conjunctival microcysts in the most prominent area of filtering bleb on the next day after the procedure (see Fig. 4). These non-tissue sub-epithelial structures are not detected under normal conditions. It is hypothesized that microcysts are filled with aqueous humor which enters them due to its active movements in subconjunctival space. When evaluating long-term hypotensive effect, microcysts are considered as a good prognostic factor [20].

No choroidal effusion was identified by ophthalmoscopy with the pupil dilated. Posterior segment OCT (RT-Vue-100, Optovue, Fremont, CA) was performed to reveal choroidal folds. Macular Cross-line scan detected neither structural defects, retinal and choroidal folds nor intraretinal fluid (see Fig. 5). This enabled to discontinue cycloplegic therapy leaving anti-inflammatory eye drops only.

The patient was examined twice during the next ten days, no visible changes in the parameters under control were observed.

Week 2. Preventive re-needling

In 2 weeks following the needling revision, conjunctival redness slightly increased due to the dilation of large venous vessels. IOP level was 12.1 mm Hg. To maintain hypotensive effect and to avoid further excessive scarring, re-needling with the above-mentioned drugs and bleb wall destruction was performed. Eye drop regimen was the same (Tobradex® + Nevanac®).

Week 4. Final examination

The patient was examined three times between week 2 and week 4, no negative changes were observed. Five weeks later, bleb status was considered favorable to prognosis (WBCS was 9 points, conjunctival redness was 8%) (see Fig. 6).

The patient reported no ocular discomfort. IOP was 13.2 mm Hg. This case could be interpreted as a refractory one, therefore, topical steroid therapy (Maxidex® one or two times a day) was continued within the next month. The treatment was self-discontinued due to the forced departure for domestic reasons.

DISCUSSION

Pathologic processes in subconjunctival space following the surgery are well-studied. Classic reparation with acute inflammation, proliferation and tissue remodeling develops in this site [21, 22].

On the next day after the surgery, hemostasis at the surgical site is secured. Active autoimmune inflammation resolves by the end of the first week. Migration and proliferation of subconjunctival fibroblasts are maximum on day 3-5 and gradually decrease by the end of the first week. Collagen matrix synthesis (maximum on day 7) may continue up to 2 months [23].

Therefore, it is obvious that the first 7 days are critical to the healing since active anti-inflammatory and anti-scarring processes may significantly impact hypotensive effect.

Patient non-compliance as well as inadequate prevention of excessive scarring in the early postoperative period may subsequently reduce hypotensive effect.

If aqueous humor drains through the scleral flap, scar tissue forms around the trabeculectomy site (so-called ring of steel) in 3-4 weeks after the surgery. This ring-shaped fibrosis restricts filtering bleb and results in late IOP elevation. By this time the injections of steroids and cytostatic agents near to the bleb site without bleb wall destruction will have no effect.

However, bleb needling revision without drug administration cannot provide long-term IOP lowering since the third through fifth postoperative weeks are a «hot» inflammatory reparative period which requires active anti-inflammatory therapy.

Modern international standard of glaucoma filtering surgery includes intraoperative use of cytostatic agents [1] and active early postoperative management, i.e., increasing steroid eye drops use in the presence of significant vascularity and corkscrew vessels, subconjunctival FU injections for encapsulated filtering bleb with corkscrew vessels, VEGF inhibitors use for excessive vascularity [Grehn F., 2014].

Despite common recommendations on dosages, routes of administration, and adjustment of topical drug dosages, individual clinical cases are unique by subconjunctival space anatomy, postoperative autoimmune inflammation intensity, and outflow pathways topography. Considering this, clinicians began to develop custom approach to prolong hypotensive effect in each patient.

Bleb needling revision following glaucoma surgery is introduced into clinical practice of Research Institute of Eye Diseases (Russian Academy of Medical Sciences) being an essential part of postoperative management. Hundreds of procedures are performed each year.

In the case described above, complex needling with mechanical bleb wall destruction and subconjunctival injections of anti-inflammatory and cytostatic drugs was performed.

On day 1, topical anti-inflammatory and hypotensive therapy as a part of preparation for needling revision was prescribed since filtering bleb was considered inflamed and hyperemic with significant early scarring.

Medication choice for postoperative ocular hypertension is of great importance as well. In primary patients, prostaglandin analogs are first-line drugs due to their efficacy and safety. However, these agents are known to dilate conjunctival vessels. In early post-op period, this effect is undesirable and promotes plasma transudation into surrounding tissues. This stimulates reparative processes in filtering bleb site but also provokes macular edema when IOP is relatively low. Pilocarpine, a drug that increases vascular permeability, should be avoided for the same reason. Topical carbonic anhydrase inhibitors (if necessary, combined with beta blockers) are the drugs of choice. When multiple drops are used, fixed-dose combination is recommended. We prefer a drug with optimal pH which provokes minimal eye irritation (Azarga®). These aspects should be considered when prescribing complex anti-inflammatory therapy.

In relatively normal IOP, the destruction of junctions between sclera and conjunctiva with a needle makes filtering bleb more diffuse. Dexamethasone injection (0.4 ml) forms a large cavity for aqueous humor drainage and provides anti-inflammatory effect. FU inhibits fibroblast proliferation and collagen synthesis thus decreasing reparative processes.

Anti-VEGF treatment has both an early and late effect. On the first day after the injection, the drug normalizes microcirculation by reducing vascular permeability. As a result, conjunctival redness decreases. This effect lasts up to 2 weeks. If the inflammation is still in progress, partial dilation of larger venous capillaries is observed. In this case, subconjunctival injection may be repeated. This resembles the principles of anti-VEGF therapy for wet AMD that involves repeated intravitreal administrations of the drug [24-26]. Late effect is the inhibition of VEGF189 and VEGF121 which results in fibroblast production decrease.

In refractory cases, long-term (for 4-5 months) instillations of steroid eye drops are recommended by European experts.

Therefore, current armamentarium of glaucoma management includes a number of techniques and medications. Their appropriate use significantly increases the efficacy of modern glaucoma filtering surgery.

REFERENCES

1. Bettin P., Khaw P.T. Postoperative management of penetrating and nonpenetrating external filtering procedures. Glaucoma Surgery. Dev. Ophthalmol. 2012; 50: 48-63.
2. Shmyreva V.F., Petrov S.Yu., Antonov A.A., Pimenidi M.K. [Controlled cytostatic therapy in the early postoperative period after glaucoma surgery (preliminary report)]. Kontroliruemaya tsitostaticheskaya terapiya v rannie sroki posle antiglaukomatoznoi khirurgii (predvaritel'nye rezul'taty). [Annals of ophthalmology]. Vestnik oftal'mologii 2007; 1: 12-14. (in Russ.).
3. Singh R.P., Goldberg I., Mohsin M. The efficacy and safety of itraoperative and/or postoperative 5-fluorouracil in trabeculectomy and phacotrabeculectomy. Clin. Experiment. Ophtalmol. 2001; 29 (5): 296-302.
4. Senger D.R., Galli S.J., Dvorak A.M., Perruzzi C.A., Harvey V.S., Dvorak H.F. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science. 1983; 219: 983-985.
5. Berkovic A., Sirois M.G. Vascular permeability induced by VEGF family members in vivo: Role of endogenous PAF and NO synthesis. J Cell Biochem. 2007; 100 (3): 727-737.
6. Ferrara N. Molecular and biological properties of vascular endothelial growth factor. J Mol Med. 1999; 77: 527-543.
7. Gavard J., Gutkind J.S. VEGF controls endothelial-cell permeability by promoting the beta-arrestin-dependent endocytosis of VE-cadherin. Nat Cell Biol. 2006; 8: 1223-1234.
8. Budzinskaya M.V. [New approach to subretinal neovascular membrane diagnostics and treatment]. Sistema novykh podkhodov k diagnostike i lecheniyu subretinal'noi neovaskulyarnoi membrany. [Med.Sc. D. thesis]. Moscow, 2011. Dissertatsiya na soiskanie uchenoi stepeni doktora meditsinskikh nauk. (in Russ.).
9. Budzinskaya M.V., Pogoda T.V., Strelkova I.D., Chikun E.A., Schegoleva I.V., Kazaryan E.E., Galoyan N.S. [The impact of genetic mutations on the subretinal neovascularization clinical picture. Report № 2. The role of HTRA и VEGF genetic polymorphism]. Vliyanie geneticheskikh mutatsii na klinicheskuyu kartinu subretinal'noi neovaskulyarizatsii. Soobshchenie 2. Rol' polimorfizmov genov HTRA i VEGF. [Annals of ophthalmology]. Vestnik oftal'mologii 2011; 4: 9-16. (in Russ.).
10. Karp J.E., Broder S. Molecular foundations of cancer: new targets for intervention. Nat. Med. 1995; 4 (1): 309-320.
11. Bochmann F., Kaufmann C., Becht C.N., Guber I., Kaiser M., Bachmann L.M., Thiel M.A. ISRCTN12125882 – Influence of topical anti-VEGF (Ranibizumab) on the outcome of filtration surgery for glaucoma – Study Protocol. BMC Ophthalmol. 2011; 11: 1.
12. Kahook M.Y. Bleb morphology and vascularity after trabeculectomy with intravitreal ranibizumab: a pilot study. Am J Ophthalmol. 2010; 150 (3): 399-403.
13. Horsley M.B., Kahook M.Y. Anti-VEGF therapy for glaucoma. Curr Opin Ophthalmol. 2010; 21 (2): 112-117.
14. How A., Chua J.L., Charlton A., Su R., Lim M., Kumar R.S., Crowston J.G.,

Wong T.T. Combined treatment with bevacizumab and 5-fluorouracil attenuates the postoperative scarring response after experimental glaucoma filtration surgery. Invest. Ophthalmol. Vis. Sci. 2010; 51 (2): 928-932.
15. Sengupta S., Venkatesh R., Ravindran R.D. Safety and Efficacy of Using Off-label Bevacizumab Versus Mitomycin C to Prevent Bleb Failure in a Single-site Phacotrabeculectomy by a Randomized Controlled Clinical Trial. J. Glaucoma. 2012; 21 (7): 450-459.
16. Klettner A., Roider J. Comparison of bevacizumab, ranibizumab, and pegaptanib in vitro: efficiency and possible additional pathways. Invest Ophthalmol Vis Sci. 2008; 49 (10): 4523-4527.
17. Camejo L., Noecker R.J. Bleb Needling. Glaucoma Today. 2007.
18. Petrov S.Yu. [Bleb classification]. Klassifikatsii fil'tratsionnykh podushek. [National Journal glaucoma]. Natsional'nyi zhurnal glaukoma 2014; 13 (3): 85-98. (in Russ.).
19. Petrov S.Yu., Novikov I.A., Dugina A.E. [Methods for assessing the functional state of the filtering bleb after glaucoma surgery]. Sposob otsenki funktsional'nogo sostoyaniya fil'tratsionnoi podushki posle antiglaukomatoznoi operatsii. [RU patent]. Patent na izobretenie 2423069. 19.11.2009. (in Russ.).
20. Addicks E.M., Quigley H.A., Green W.R., Robin A. L: Histologic characteristics of filtering blebs in glaucomatous eyes. Arch Ophthalmol. 1983; 101: 795.
21. Lebedev O.I. [The concept of excessive scarring after glaucoma surgery]. Kontseptsiya izbytochnogo rubtsevaniya tkanei glaza posle antiglaukomatoznykh operatsii. [Annals of ophthalmology]. Vestnik oftal'mologii 1993; 1: 36-39. (in Russ.).
22. Shmyreva V.F., Petrov S.Yu., Makarova A.S. [Causes of long-term decrease of glaucoma surgery hypotensive effect and possibilities of its enhancement]. Prichiny snizheniya otdalennoi gipotenzivnoi effektivnosti antiglaukomatoznykh operatsii i vozmozhnosti ee povysheniya. [Glaucoma]. Glaukoma 2010. 2: 43-49. (in Russ.).
23. Wong J., Wang N., Miller J.W., Schuman J.S. Modulation of human fibroblast activity by selected angiogenesis inhibitors. Exp.Eye. Res. 1994; 58: 439-451.
24. Budzinskaya M.V., Gurova I.V. [Subretinal neovascular membrane in patients with age-related macular degeneration]. Subretinal'naya neovaskulyarnaya membrana pri vozrastnoi makulyarnoi degeneratsii. [Annals of ophthalmology]. Vestnik oftal'mologii 2006; 122 (4): 49-54. (in Russ.).
25. Budzinskaya M.V., Pogoda T.V., Generosov E.V., Chikun E.A., Gurova I.V., Schegoleva I.V., Sizova M.V. [Modern farmacogenetical approach to treating age-related macular degeneration]. Sovremennye farmakogeneticheskie podkhody k lecheniyu vozrastnoi makulyarnoi degeneratsii. [Annals of ophthalmology]. Vestnik oftal'mologii.2013; 129 (5): 127-135. (in Russ.).
26. Budzinskaya M.V., Gurova I.V., Schegoleva I.V., Loshenov V.B., Shevchik S.A., Kuzmin S.G., Vorozhtsov G.N. [Combined therapy of exudative age-related macular degeneration]. Kombinirovannaya terapiya ekssudativnoi formy vozrastnoi makulyarnoi degeneratsii setchatki. [Photodynamic therapy and photodiagnostics]. Fotodinamicheskaya terapiya i fotodiagnostika. 2013; 1: 20-24. (in Russ.).