Intracameral bevacizumab administration in trabeculectomy surgery.

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Description

Traditional glaucoma filtration surgery, namely guarded trabeculectomy, remains the most effective surgical method of lowering intraocular pressure and is widely utilized in the treatment of moderate to advanced glaucoma despite the risks associated with the procedure and the tedious follow-up [1]. Surgical success is associated with the ability to predict and/or modulate the wound healing response driving episcleral fibrosis and limiting thereby the effective filtration area. Maintenance of adequate aqueous flow to the subconjunctival space relies on a fine balance between aqueous egress through the trabeculectomy ostium, as determined by the size of the ostium and the resistance provided by the trabeculectomy flap, and the innate ability of the eye to recruit fibroblasts that results in subconjunctival fibrosis. Initial excessive aqueous flow through the trabeculectomy ostium is associated with hypotony and/or early bleb leaks as episcleral fibrosis cannot provide significant resistance to the egress of aqueous in the early post-operative period.

At a later stage intrinsic and migratory fibroblasts assume an important role. Fibroblasts proliferate, transdifferentiate into myofibroblasts, and produce extracellular matrix proteins (i.e., collagen) [2]. These cells are responsible for the corkscrew appearance of conjunctival blood vessels [3] and can cause conjunctival retraction especially in limbus based trabeculectomies. Episcleral fibrosis provides increasing resistance to outflow, which we attempt to counterbalance either by increasing aqueous flow with laser suture lysis or removal of releasable sutures that keep the episcleral trapdoor shut, or by modulating episcleral fibrosis by the postoperative administration of 5-fluorouracil (5-FU). The timing and the intensity of episcleral fibrosis relies among others on several factors such as age, the pre-operative state of the conjunctiva (eyes that have been exposed to preserved glaucoma drops for a prolonged period respond with more aggressive fibrosis) [4], the inflammatory response that is associated with surgery (combined phacotrabeculectomy cases elicit a stronger wound healing response) and the effective dose of mitomycin C (MMC) administered during surgery. Antimetabolites (5-FU and MMC) have been introduced almost 3 decades ago and have certainly improved trabeculectomy survival rates at the expense however of a higher proportion of thin-walled cystic blebs that predispose to late complications such late bleb leaks, blebitis or endophthalmitis [5,6].

There are only very few prospective, randomized clinical trials that investigate the potential role of other pharmacologic means to modulate wound healing after trabeculectomy [7]. In the prospective, well-designed, single surgeon, comparative, interventional case series by Kopsinis, et al. [8] the authors investigate the use of a novel approach to wound healing modulation after trabeculectomy. They compare the outcomes of trabeculectomy surgery performed in a cohort of 100 open angle glaucoma eyes) half of which receive the conventional off-label approach, namely intraoperative 0.02% MMC application with sponges for 2 minutes followed by 5-FU injections post-operatively as necessary while the reminder receives a single intracameral administration of 1.25 mg bevacizumab (Avastin, Genentech, San Francisco, CA) with post-operative 5-FU injections but without MMC. Bevacizumab is a recombinant, humanized, monoclonal antibody directed against the Vascular Endothelial Growth Factor (VEGF), it has been extensively used in Ophthalmology and there is sufficient data regarding its safety even after repetitive intraocular administrations [9]. VEGF is upregulated in aqueous humor of patients with glaucoma and appears to be playing an important role in angiogenesis, fibroblast proliferation and vascular permeability [2,8,10]. It therefore drives the episcleral fibrosis response and promotes inflammation

One of the potential advantages of bevacizumab may be that it affects vascular density and capillary leakage at the surgical site without hindering the proliferation of rapidly proliferating cells such as corneal epithelial cells. It may therefore induce less corneal punctate epithelial erosions and be associated with less discomfort and faster visual rehabilitation compared to antimetabolites. The key conclusions of the study are that bevacizumab is equally effective as intraoperative MMC application with the two groups achieving similar pressure reduction (15.4 ± 3.8 mmHg vs. 15 ± 3.4 mmHg), medication requirements (0.6 ± 1.1 vs. 0.5 ± 1 substances) and survival of the procedure by widely employed criteria [11] (86% vs. 90% qualified success) after three years of follow-up. Similarly, there is no significant difference in the incidence of commonly encountered early or late post-operative complications. The main strengths of the study are the straight-forward study protocol, the randomization of study participants, the longer compared to other studies follow-up [12-16] and the fact that no patient was lost to follow-up. Limitations of this study include the relatively small sample size, the lack of masking during the follow-up period and the fact that this represents a single surgeon's experience. Furthermore, unanswered questions remain after this pilot study and are pertinent to the optimal dosing and route of administration (intracameral vs. subconjunctival vs. topical) of bevacizumab, and the possible effect on surgical survival of repetitive administrations of this agent in the post-operative period especially as the bevacizumab group may achieve a larger IOP reduction early on after the procedure in this and in other studies [8,16]. Moreover, the combined use of antimetabolites (MMC) and ant-VEGF molecules may prove to be complementary in action.

Conclusion

Finally, the study is not evaluating bleb morphology objectively by a masked investigator which may allow us to infer effects of bevacizumab on late and uncommon complications such as late bleb leaks. These shortcomings however do not limit the internal validity of the study conclusions but call for a well-designed larger multicenter randomized clinical trial.

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