



Can we improve function in glaucoma by trabeculectomy?

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Since glaucoma was recognized as an eye disease related to elevated intraocular pressure (IOP) in the 19th century, treatment was mostly directed towards lowering IOP to a “normal” range (1). In the 1960ies, “guarded” filtering procedures were developed in order to reduce complications from “unprotected” operations such as Elliot’s trephination or Scheie’s procedure. Over 50 years, trabeculectomy has been considered the standard filtering procedure for advanced or progressing glaucoma cases to achieve long lasting low IOPs. Trabeculectomy has the advantage of reducing IOP into the low teens or upper single digits which is considered a safe “target” range suited to halt or reduce visual field (VF) deterioration. However, the complications of trabeculectomy are still considerable, such as hypotony, choroidal effusion or subchoroidal bleeding, and long-term success is challenged by excessive wound healing resulting in obliteration of the new outflow routes.

The different approaches of glaucoma treatment—medication, laser, and surgery—have been reviewed for effectiveness and outcome (2-4). In most of these studies, filtering surgery achieved lower IOPs than medication or laser. Surgical studies usually take IOP as a primary outcome measure, and not function such as VF. For the patient, however, the VF is more relevant as it is related to quality of vision.

Up to nowadays, the current view has been that retinal ganglion cell (RGC) function cannot be restored or improved because RGCs irreversibly die by apoptosis. However, improvement of retinal function has already been suggested by George Spaeth (5) as a measure of successful glaucoma treatment. According to his hypothesis, glaucoma is only adequately treated if improvement occurs.

During the past decades, quantitative VF evaluation often was based on global indices such as mean defect (MD), glaucoma index (GI) (6), Bebié curve (7), or selected integral areas of the VF test (8,9). However, global indices hide scotomata in small limited areas, which are typical for early glaucoma. The pointwise linear regression analysis, initially developed at Moorfields Eye Hospital was an approach to overcome these problems (10,11).

The paper by Caprioli *et al.* (12) evaluated the individual changes of small test locations over time using a similar test strategy. The hypothesis of improvement of the VF was addressed in patients that had sufficient VF follow-up before and after trabeculectomy to allow statistical significant regression analysis (follow-up ≥ 4 years and ≥ 4 VF examinations before trabeculectomy, and follow-up ≥ 4 years, ≥ 4 VF examinations after trabeculectomy). They also used statistical methods to remove outliers and tested linear versus nonlinear regression for follow-up. Using clinical data, the paper of Caprioli *et al.* (12) provides evidence that the VF can improve after successful trabeculectomy.

Here is a short summary of the results:

- (I) A total of 74 eyes out of 1,290 trabeculectomies fulfilled the selection criteria. As this analysis was retrospective using a cohort of consecutive cases, the authors compiled also a comparative group of non-operated (medically treated) eyes of similar IOP and VF damage with the same inclusion criteria, namely ≥ 8 VFs over the period of ≥ 8 years, and separated the first half period (4 years) and the second half period (4 years) in order to test VF progression in two separate periods comparable

to the pre- and postoperative periods of the trabeculectomy cases;

- (II) The comparison evaluated pre- and postsurgical rates of change of each single VF location in order to define improvement or decay by statistical regression analysis (linear or non-linear). They also evaluated the number of individual VF spots that decayed or improved and compared these numbers to the results of the comparative group (first and second half of the 8-year period). Decay or improvement could thus be quantitatively compared in each VF location of a single patient and within the whole cohort before and after the intervention.

The advantage of using trabeculectomy cases (and not medically treated cases) is (I) the clear time definition of the therapeutic “intervention”; (II) the amount of IOP lowering; and (III) the independence from the compliance as compared to patients who are medically treated.

Four major results can be learned from this paper:

- (I) The mean decay rate of the VF was slowed down after surgery by the factor of ≥ 4 . In numbers, the mean decay rate in the trabeculectomy group was $-2.4\%/year$ before surgery and $-0.6\%/year$ after surgery ($P < 0.001$), or -0.7 *vs.* -0.1 dB/year. In contrast, the comparison group had no significant difference in the decay rate of the first versus the second half of follow-up;
- (II) Significantly more VF locations improved after trabeculectomy as compared to before surgery and to the comparison group. In this type of analysis, the number of all test locations with improvement of the trabeculectomy group [3,064] and the comparison group [2,897] were counted, except those which had a zero sensitivity (blind spot and absolute scotomata). In the trabeculectomy group, 30% of points showed improvement before surgery, and 44% showed improvement after surgery, whereas in the comparative group the percentage remained equal in the first and the second half of the observation period (34% *vs.* 35%). A total of 80% of eyes after trabeculectomy had five VF locations that showed significant improvement of sensitivity on non-linear regression analysis, and 57% of eyes after trabeculectomy had ten or more locations that improved. This was also significantly better than in the comparison group. These two analyses clearly provide evidence that the tendency

of VF locations to improve was greater after trabeculectomy than before trabeculectomy;

- (III) The number of improving locations of the VF was moderately correlated with the magnitude of IOP reduction. If the difference between the last three preoperative averaged IOPs and the first three postoperative IOPs was plotted against the number of improving points, a correlation of 0.32 ($P = 0.005$) was found. The mean IOP and the peak IOP decreased from 14.7 to 10.0 mmHg and from 18.8 to 13.6 mmHg, respectively;
- (IV) The average sensitivity became stable after trabeculectomy, but there was a steplike decrease of sensitivity immediately after trabeculectomy, which was followed by the flatter, more stable curve. Although the averaged progression curve was flatter after trabeculectomy, the first postoperative sensitivity after surgery was lower than the last preoperative sensitivity (Figure 4 of the paper). This step towards a lower sensitivity after trabeculectomy is a common experience for glaucoma surgeons. We do not know whether this step is due to postoperative change of refractive media, corneal surface problems, transient general depression of function of RGCs, limited VF test performance after surgery, or other mechanisms. When comparing preoperative MD at the beginning of the study to the last postoperative MD, the trabeculectomy group lost -3.5 dB (range, -7.2 to -10.7 dB) whereas the comparison group lost only -2.6 dB (range, -5.6 to -8.2 dB) during the same time period. Despite the higher number of improving test locations, the average sensitivity decreased more in the surgically treated group as compared to the medically treated group. On the other hand, in my experience, quite a number of patients report subjective improvement of their long-term visual perception (quality of vision) after surgery. It is still unknown, whether the improvement of individual VF locations contributes to the subjective improvement quality of vision of the patient.

Of course, the high variation of individual test locations that improve versus those that decay is a challenge. In this study, 70% of locations decayed and 30% improved preoperatively, whereas 56% decayed and 44% improved postoperatively. Although this difference was statistically significant, one must be aware that the reproducibility of

measurement in an individual patient may be critical from one to the next VF test in a busy routine clinic. Oblique head position, cyclorotation, attentiveness of the patient at different visits etc. may lead to considerable variability.

What are the cellular mechanisms that allow RGC function to recover?

Retrograde axoplasmic flow inhibition at the level of the lamina cribrosa has been considered the primary step to deprive RGC somata from surviving signals sent from the lateral geniculate nucleus synapses (i.e., neurotrophins). This deprivation triggers irreversible cell death (apoptosis). On the RGC level, electrical transmission of information (propagation of axon potentials) is very sensitive to reduced oxygen supply, but can restore after long periods of oxygen deprivation (13). Electrical signal transmission of the axon is different from axonal survival regulated by its nutritional support from axoplasmic flow. Several observations support the view that ganglion cells can survive while electrical function is suspended when borderline nutritional support still available to the axon. For example, in pituitary tumor, VF defects are partly or completely reversible when pressure by the tumor is removed (14). The photopic negative response of the electroretinogram, a signal associated with the RGC function, improved in those eyes where the IOP was lowered $\geq 25\%$ (15). In single cell recordings of retinal axons, electrical activity of the axon (action potentials) can resume even after longer periods of IOP induced ischemia (13,16,17). In such a scenario the RGC function may resume after lowering of IOP, in particular when lowered to a low-normal range by surgery.

What can the general glaucoma specialist learn from the study?

- (I) Improvement of VF sensitivity after surgical reduction of IOP (mean postop IOP approx. 10.0 mmHg) occurs in significantly more locations than in a comparative group with less pronounced IOP lowering by medical therapy. This emphasizes the need of low normal pressures to halt or even improve glaucoma damage;
- (II) The paper is a proof of principle that real recovery of function (probably RGC function) can occur, with the implication that “low IOP pays off”;
- (III) The evidence of improved function after trabeculectomy speaks in favor of surgical methods

with high IOP lowering potential in advanced or progressive glaucoma cases, such as trabeculectomy or other filtering procedures;

- (IV) Stabilization (or improvement) of the VF only pays off at a long-term, while surgery for patients with short life expectancy must be carefully considered. In this study, during the ≥ 8 year follow-up period (4 years before and 4 years after surgery), the total loss of sensitivity was still higher (-3.5 dB) in the trabeculectomy group than in the comparative group (-2.6 dB). This was due to a “step” to lower average sensitivity immediately after trabeculectomy, not due to increased or persistent decay process. Perhaps we must tell our patients before surgery that the possible improvement may not be instantaneous;
- (V) There is a lot of variation of the individual test location sensitivities in a glaucomatous VF, due to various factors. However, analyzing the improvement versus decay of individual test points of the VF may be helpful to indicate glaucoma surgery in an individual patient.

The paper of Caprioli *et al.* (12) is a milestone telling us that (I) improvement of compromised VF areas can be achieved and (II) low normal IOPs as obtained by trabeculectomy are a prerequisite to reach this goal.

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