



# Visual function restoring after trabeculectomy: between dream and reality

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Glaucoma is characterized by the progressive degeneration of the optic nerve head (ONH) and retinal ganglion cells (RGCs). RGCs can be divided into basic regions, including the axon and synapse, the dendritic arbor, and the cell body (1). These compartments can independently be affected by degeneration processes and cause damage of the ONH (1,2).

An established theory considers intraocular pressure (IOP) the main responsible for axon damage, mainly at the lamellar region, where the axons of the RGCs exit the globe as they enter the optic nerve. At this level elevated IOP strains the axon's fiber and causes molecular and functional changes to the resident cell population of the tissue. Particularly, blockage of axoplasmic flow, and interference in retrograde neurotrophin transport to RGCs, leads to cell death. Moreover, Hernandez (3) has identified the astrocytes as the key cell type involved in this process at the ONH and has shown astrocytes to be activated by increased IOP; the loss of their support functions may lead to axons becoming unable to sustain energy dependent processes such as axonal transport (4).

Acute injury, such as axotomy, is rare. Probably, the level of damage to most axons is sub acute, and they are likely to retain connection and some level of communication with the ganglion cell soma.

Loss of axonal function leads to the activation of degenerative atrophy of the RGC bodies. Ganglion cell somas misses neurotrophic input from target neurons in the brain, and failure of axonal transport results in activation of apoptosis (2).

Another important consideration is that ganglion cells

initially damaged at the level of the ONH, produce a chain of events that leads to damage to the surrounding, normally healthy ganglion cells. This effect is called secondary degeneration and means that the complete pathology of ganglion cell death and optic nerve degeneration involves both an axogenic component (leading to primary degeneration) and a somatic component (secondary degeneration).

The mechanism of secondary degeneration is not clear but it seems that dying cells affect other cell types in the retina, principally macro and microglia (5). If secondary degeneration is a real phenomenon, then it provides an important opportunity to inhibit this process and preserve ganglion cells that still have good axons and may be converted into a functional state.

Obviously, accepting this pathogenic mechanism, it is possible to better explain why after surgery is possible to observe short and long term visual function restoring.

RGCs function may be measured using pattern electroretinogram (ERG) optimized for glaucoma (PERGLA), color vision testing and contrast sensitivity; published literature confirmed short-term improvement of these cells after surgery (6-10). It has been demonstrated a direct matching between pattern ERG amplitude and percentage improvement in visual field (VF) sensitivity observed in patients younger than 70 years (8). Additionally, reducing IOP in patients with glaucoma or with ocular hypertension is associated with an increased amplitude of the photopic negative response (10).

Short-term functional improvement could also be related with a structural change; our group described an increased retinal nerve fiber layer (RNFL) thickness respectively

3 months and 6 months after trabeculectomy; but any statistically significant change was observed in term of rim area and rim volume nor cup depth, cup area and cup volume and cup to disc ratio. The compression on the axons is relieved by IOP reduction and it could be postulated a resultant recover of their shape and size and consequently an increased RNFL thickness. Beside these interesting findings, our study misses to demonstrate a significant amelioration of RGCs function (11).

Joseph Caprioli recently published a paper showing how, also after long term follow-up time, trabeculectomy slowed perimetric decay and improved visual function in glaucomatous patient.

Seventy four eyes of sixty four patients with at least 4 years of follow up, before and after trabeculectomy, and with  $\geq 4$  reliable VF examinations, before and after surgery, were enrolled. In order to obtain trusty results a comparison group matched for baseline damage, number of VF test and follow up was considered.

Results of the paper showed the mean rate of change for all VF locations slowed to  $0.10\% \pm 13.1\%$ /year after surgery ( $P < 0.001$ ). In the trabeculectomy group, after surgery, it's visible an improvement in 44% of locations versus a decay in 56% of locations. The differences between the trabeculectomy and the comparison groups were significant ( $P < 0.0001$ , chi-square test).

The amount of IOP reduction correlated with the excess number of VF locations that exhibited long-term improvement postoperatively ( $P = 0.009$ ). In the trabeculectomy group, 57% of eyes had  $\geq 10$  improving VF locations postoperatively (12).

The results of this paper were confirmed also by previous studies (13-17) but all of them were affected by some limitations as the small number of VF examinations considered, the test-retest variability in advanced glaucoma, and by regression to the mean. The latter could be better explained considering that depressed points are more likely to improve than to decay.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) (17), however, demonstrated an improvement in VFs either after medical or surgical intervention at 5 years of follow up. An interesting issue for discussion could be if it's better surgical or medical therapy to slow glaucoma progression. The answer is not easy and literature actually fails to be clear. It is well known that before the introduction of prostaglandin analogues the reduction of IOP obtained with surgery, particularly with trabeculectomy, was greater and last for longer time. Results from the CIGTS demonstrated a greater IOP

reduction after trabeculectomy (40%) than with medical treatment (31%) after 4 years of follow up; anyway surgical patients suffered of a reduction of their quality of life; especially during the first month after surgery but this difference disappeared later during follow-up time; this group had also a greater percentage (17%) of cataract compared with patients treated pharmacologically (17). In terms of visual function and VF performance any difference has been observed between initial surgery or initial medications; beyond this, the clinical and cost-effectiveness of contemporary medication (prostaglandin analogues, alpha 2-agonists and topical carbonic anhydrase inhibitors) compared with primary surgery is still not known (18).

Nowadays, IOP reduction achieved with surgery is affected by years of medical therapy with eye-drops that have a serious impact on the conjunctiva and may determine an earlier failure of the surgical treatment. In addition, it has to be considered, the effect of preservatives that can cause corneal and conjunctival toxicity, including cell loss, disruption of tight junctions, apoptosis and preapoptosis, cytoskeleton changes, and immunoinflammatory reactions (19,20). Practically, after surgery the target IOP is achieved but for a shorter period of time and this may cause a progression of the disease with a deterioration of the visual function. A very recent paper indicates some major risk factors for trabeculectomy failure: glaucoma type, previous ophthalmic surgery, glaucoma medication use  $\geq 3$  years and 4 glaucoma medications use pre-trabeculectomy; the authors interestingly describe also an addictive effect of these risk factors, as a result people with 3 to 4 factors has greater risk of failure (21).

The correct timing of surgery is another crucial point of discussion; the common indications for surgical treatments have been reported: the failure of other forms of therapy, like medicines or laser, all cases where other forms of therapy are not suitable (e.g., where compliance and side-effects are a problem), all cases where topical medications and laser can't reach the target pressure and in cases which have such advanced glaucoma and high IOP at presentation that other forms of treatment are unlikely to be successful (22).

In the past, some studies have suggested primary trabeculectomy to be superior to medical treatment in terms of field survival, but these results were affected by the limited number of medications available and by the absence of automated statistical analysis software in the perimeter. On the contrary, more recent trial suggested that medications and surgery are equally effective in reducing field progression and we have already discussed

about this in the previous paragraph (17). The decision for surgery should be balanced considering the risks and benefits of each individual patient; target IOP, previous history, patient's risk profile, stage of the disease and quality of life should be taken into consideration by the surgeon. The final decision must be shared by the patient and the doctor and the patient should be aware of the complications of surgery such as vision loss, bleeding, infection, low eye pressure, scarring and cataract. It is important to note, however, that glaucoma surgery may be very successful at slowing glaucoma progression and achieving the target IOP. Furthermore, if glaucoma is inadequately treated it is almost certain that vision will be lost.

Finally, considering the increasing evidence of RGCs restore after surgery and the maintenance of visual function, the suggestion is not to leave surgery as the final treatment options for glaucomatous patients. Mainly, today we may use improvements of standard trabeculectomy realizing a safer procedure (23-25).

Currently, it is widely accepted that the correct management of glaucomatous patients is try to individualize the treatment for each patients and to maintain as longer as possible his visual function and the related quality of life. To reach this goal, all glaucoma surgery, not only standard trabeculectomy, but also laser treatment, non penetrating techniques, minimally invasive glaucoma surgery and tubes may represent an alternative to medical treatment. Ophthalmologist should be conscious of all these possibilities and should not be scared about that, maybe a drop initially seems less dangerous but fail to reach the real scope of the treatment.

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