Review Article

Capsula Eburnea

THERAPEUTIC APPROCHES TO GLAUCOMA: NEW INSIGHTS

Rossella Occhipinti

SUMMARY

Glaucoma is an eye disorder in which the optic nerve suffers damage, permanently impacting vision in the affected eyes and progressing to complete blindness if left untreated. It is often, but not always, associated with increased pressure of the aqueous humor in the eye. Due to its seriousness it is important to develop a therapeutic plan which is based on reducing the intraocular pressure. It is essential to evaluate the clinical situation of the patient affected by glaucoma correctly, in order to choose the most appropriate treatment for their condition. The aim of this study is to investigate current treatments for glaucoma and describe the new therapeutic approaches still being tested.

Introduction

Glaucoma is an ocular condition the essential features of which are represented by disorders of the aqueous circulation, leading to intraocular pressure (IOP) values which are usually higher than the norm. These IOP values, either on their own or together with other factors, cause degenerative phenomena of the nerve fibers at the head of the optic nerve, causing mainly perimetric sensory deficiency [1]. According to the World Health Organization (WHO), glaucoma is the cause of blindness in 4.5 to 5 million people in the world. Its prevalence rises with age, from ca. 2.4% in people over 40 to more than 7% in people over 75; there is no clear difference in prevalence between men and women [2,3]. Glaucoma can be congenital or acquired. Acquired glaucoma can be classified further as either closed-angle or open-angle. This classification is based on the process by which the outflow of aqueous humor is obstructed. Glaucoma can also be primary or secondary, depending on the presence or absence of associated factors, which have contributed to the pressure rise. In primary glaucoma the rise of the IOP is never associated to with other ocular disorders, while in secondary glaucoma a recognizable factor, either ocular or not, distorts the outflow of aqueous humor which, consequently, determines a rise of IOP [4]. Elevated IOP (>21 mmHg) is the main risk factor for glaucoma; other risk factors include markedly fluctuating IOP, myopia, a family history of glaucoma, a thin cornea, and other associated ocular pathologies, such as the pseudoexfoliation syndrome [2,3,5]. Epidemiological studies have shown that the risk of glaucoma rises by 12% with every 1 mmHg rise in IOP [6].

Diagnostic criteria

In the last few years the redefinition of the relationship between IOP and glaucoma has progressively and radically changed the approach of the eye specialist towards this disease. Indeed, for specialists themselves, providing a precise diagnostic definition is still a challenge. The measuring of IOP, the biomicroscopic evaluation of the optic nerve and

Address of the author
Department of Ophthalmology, University of Catania, Italy

***Send correspondence to**: Dr. Rossella Occhipinti, rossella6184@yahoo.it*

***Received**: March 2nd, 2011 — **Revised**: April 11st, 2011 — **Accepted**: April 18th, 2011*

the peripapillary nerve fibers and the examination of the visual field carried out with the conventional perimetric technique, are still the most important aspects in the diagnosis of glaucoma. The IOP is generally measured with applanation tonometry, which was introduced by Goldman in 1945/55. In this technique the cornea is topically anesthetized, its opex is "flattened" with a measuring head and the applied force necessary to deform it is taken as an index from which the IOP can be derived. The measured value depends not only on the examiner, but also on the biochemical properties of the cornea, including its thickness. The newer tonometric techniques include rebound tonometry, which does not require anesthesia of the cornea and dynamic contour tonometry, which is more cumbersome but less susceptible to inaccuracy resulting from the properties of the cornea. Goldman applanation tonometry is still considered the standard technique [5]. The variation of the biomicroscopy of the optic nerve and the peripapillary nerve fibers depend on the severity and the stage of the disease. The main signs to be investigated are: increased excavation of the papilla, loss of the neuretinal fissure, relationship between fissure-disk, relationship between excavation-disk, changes in the blood vessels internal to the optic nerves.

Current Therapies

Multi large-scale randomized studies have most convincingly shown, that local treatment – either medical or surgical – lowers the IOP and protects the visual field to a statistically significant extent in primary chronic open-angle glaucoma, normal-pressure glaucoma and ocular hypertension [2, 7-9]. In the stepwise treatment Algorithm recommended by European Glaucoma Society (EGS), pharmacological reduction of the IOP is the first stop, followed by laser surgery of the trabecular meshwork and (filtering) glaucoma surgery [10].

Medical therapy

The choice of the drug to use depends first not only on the kind of glaucoma but also on the anamnesis of the patient (for instance the presence of asthma or bradycardia). Therefore, it is necessary to have an extensive knowledge of the potential side effects of each kind of drug [11]. The family of beta-blockers is so called because of their capacity to occupy the beta-adrenergic post-synaptic receptors of the ciliary body, which are not available for the stimulant action of the adrenergic neurotransmitters, adrenalin (Epinephrine) and noradrenalin (norephinephrine). They are able to reduce IOP from 20% to 25% [12]. The progenitor of this family is *timolol* followed by *betaxolol*, *levobunolol*, *carteolol* and *metipranolol*. Their half-life is about 12 hours. They can produce ocular side effects (rare allergies, puntate keratopathy and reduced production of the lachrymal film), and systemic side effects which tend to appear during the first week of intake (bradycardia, hypotension, bronchospasm, sleep disorders, depression, reduction in libido, hallucination, fatigue, confusion, etc.). For this reason these drugs have to be avoided in patients with congestive heart failure, second or third grade heart failure, bradycardia, asthma and obstructive diseases of the respiratory tract. It is most important not to take beta-blockers before going to bed because they cause a sharp decrease in blood pressure while the patient is sleeping, reducing the perfusion of the optic nerve and causing visual deterioration [4]. These drugs are topical inhibitors of carbonic anhydrase and inhibit the action of the enzyme carbonic anhydrase of the epithelial cells of the ciliary body; however, their mechanism of action is still being discussed, as there is some conflicting scientific evidence [1]. The progenitor molecule is *acetozolamide* followed by *dorzolamide* and *brinzolamide*. The hypotonic result of acetozolamide is 40% but it doesn't cause significant hypotonic effects until its dosage inhibits at least 98% of the enzyme activity. For this reason, and also due to the fact that this molecule is given systemically, it causes many side effects, for example: kidney stones, polyuria, nicturia, gastric and intestinal disorders, diarrhea, hypokalemia, acidosis, paraesthesias, etc. Due to the presence of so many side effects concerning acetozolamide, two other molecules have been developed, dorzolamide and brinzolamide in collyrium (without side effects due to the systemic administration). The two molecules are able to reduce IOP from 20% to 25%. The side effects associated with the topical administration are: sensation of bitter aftertaste and allergic conjunctivitis, while the systemic side

effects are absent. In addition, it must not be forgotten that these drugs must be used cautiously in patients with corneal endothelial dysfunction, as they can cause decompensation [4]. However, it is important to point out the positive side effects on arterial circulation meaning that they can be used in order to better the circulation of the head of the optical nerve. The effectiveness of this treatment in improving the evolution of the glaucoma, still has to be proved by clinical study [1]. Parasympathomimetic drugs work by stimulating the muscarinic receptors of the papillary sphincter and the ciliary body. One such drug, *pilocarpine,* has been known since the second half of 19th century as a drug capable of reducing IOP, but today, due to its important ocular side effects: myosis serrata, accomodative spasm, decrease in the anterior chamber, "pseudo-traction" effect on the retinal periphery and 3-4 administrations per day, it has been discarded in favour of more effective and better tolerated drugs. For this reason, mostly pilocarpina is used with beta-blockers, as an alternative *carbachol* is used as it has fewer side effects. Both molecules, pilocarpine and carbachol have the capacity to reduce IOP by around 20%. The analogous of prostaglandin (PGA) are the class of drugs which are most effective in lowering IOP, as they have the capacity to reduce it by around 33% [12]. The advantages offered by this class of drugs are: a very short systemic half-life, and therefore a very low rate of systemic side effects; prolonged pressure-lowering effect, pressure reduction through improved outflow (uveoscleral and trabecular), and application only once a day, usually in the evening (compliance) [5]. The molecules which are available nowadays are *latanoprost*, *travoprost* and *bimatoprost*. Among the side effects are hyperpigmentation of the iris (in 50% of patients) [13], especially on green-brown iris and, in addition, a high percentage of patients can develop hypertrichosis, conjunctival hyperemia and sensation of a foreign body. The risk of cystaid macular edema (water deposition in the middle of the retina, impairing central visual acuity) due to PGA treatment is uncertain as far as can be determined from current data. If macular edema develops under PGA treatment, an attempt should be made to discontinue the treatment. In the author's personal experience, however, the risk of macular edema is not so high so as to necessitate the discontinuation of PGA before intraocular surgery. A recently published retrospective study supports our opinion [5,14]. It should be noted that these drugs are contraindicated in pregnancy because studies on animals have proved potential teratogenic effects. Symphatomimetic drugs work through two mechanisms: both through lowering the production of aqueous humor and increasing the outflow of aqueous humor. They both inhibit the release of norephinephrine from the terminal neuron which usually stimulates the production of aqueous humor and they reduce the haematic flow by vasoconstriction of ciliary arteries (a hypothesis which still has to be verified in the literature) [1]. This class of drugs includes *clonidine*, *apraclonidine* and *brimodine*. They have the capacity to reduce IOP by 25% [12]. Clonidine at 0.125% presents features of lipophilia and, for this reason, it has the capacity to enter the central nervous system and cause many side effects, for example: marked systemic hypotension and bradycardia. At an ocular level it leads to a transient conjunctival hyperemia, which is followed by a lasting vasoconstriction. Aproclonidine is a derivate of clonidine, from which it differs due to its lower lipid solubility which prevents it from easily passing through the blood-brain barrier. Moreover, its hypotonic effect obtainable with concentrations at 0.5% and 1% and it is even more marked (25%) and long lasting than clonidine's effect. Brimodine is a highly selective agonist α-2. Moreover, it has been shown to have a direct neuroprotective effect on the ganglion cells [1]. It has only ocular side effects such as allergic conjunctivitis and uveita granulomatous anterior. Finally, the last class of drugs, asthmatic agents, are used when a temporary drop of IOP is needed, which cannot be obtained by other means (for example, in the acute narrow-angle glaucoma, or before an intraocular surgery, when IOP is very high). *Glycerol*, *isosorbide* and *mannitol* are usually used. They can cause: cardiovascular overload, urinary retention, headache and mental confusion.

Laser therapy

Laser treatment plays an important role in glaucoma therapy; it can be used both in open-angle glaucoma and angle-closure

glaucoma and when it is necessary to induce an atrophy of the ciliary body. We can both increase the trabecular outflow (with Argon-laser or Yag-laser) and expand the iris-corneal-angle (gonioplasty with Argon-laser) creating a by-pass between the anterior and posterior chamber (iridotomy with Yag-laser or Argon-laser). Moreover, it is also possible to obtain an atrophy of the ciliary body (ciclophotocoagulation with Yag-laser or Argon-laser). The trabeculoplasty with Argon-laser involves the application of small burns at the trabecular level in order to help the outflow of aqueous humor and thereby lower IOP. While Yag-laser is a relatively new procedure using a 532 nm frequency, it provides the necessary energy to selectively act on the pigment of the trabecular cells, preserving the unpigmented cells and the structure. Laser trabecularplasty reduces the IOP by no more than 5-6 mmHg, a much smaller amount than filtration surgery [15]. In general this technique is being used in patients who do not tolerate the medical therapy, patients who have an IOP no higher than 25 mmHg and senior patients. Gonioplasty is the treatment of photocoagulation of the extreme iris periphery which leads to a retraction and a tissue atrophy which follows an angle expansion. It is indicated where there is a narrow-angle due to pupillary block ("a plateau iris") glaucoma or in cases of monophthalmia. Iridotomy is a continuous solution which connects the anterior chamber with the posterior one. Usually it is used with eyes characterized by a pupillary block which has caused the angle closure. Ciclophotocoagulation lowers IOP destroying part of the secreting ciliary epithelium, in this way it lowers the production of aqueous humor. However, nowadays this technique is under discussion because of its serious side effects; indeed, in 10% of the cases it causes chronic hypotonicity in 18% of the cases a total loss of visual acuity, scleral attenuation, corneal decompensation, detachment of the retina and choroid, pain and inflammation of the anterior segment, emovitreo and sympathetic ophthalmia [16].

Surgical therapy

Surgical therapy is recommended when medical therapy is not appropriate, or not tolerated, not effective or inadequately used by the patient. For these reasons glaucoma becomes uncontrolled with progressive damage. Trabeculectomy creates an artificial outflow, thanks to which aqueous humor flows out from the anterior chamber into the subconjuctival space, creating the so called " filtering swelling", helping the reabsorption of aqueous humor by the tissue and the conjunctival vessels. This is the first choice operation for patients suffering from glaucoma for whom medical therapy or laser-therapy has failed. The studies that have been carried out regarding this surgical technique have highlighted a decrease in IOP or values which does not exceed 20 mmHg [17,18]. However, the most important and frequent post-operative complications are: marked hypotone, hypo/a-hypothalamy, detachment of choroid (serous or haemorrhagic) and hypertone. However, the local intra-operating application of *mitomycin* o *5-fluororacil* is important in trabeculectomy [19]. These two compounds inhibit fibroblastic activity and so they ensure a better operative outcome. However, the application of these two kinds of drugs is not free from post-operative risks, as a small percentage of patients, 1% - 1.5%, can develop secondary endophthalmitis [20]. Trabeculotomy and gonioctomy are two techniques which are mostly used to treat congenital glaucoma. The choice between the two treatments depends on the corneal transparency, for gonioctomy to be effective a good corneal transparency is necessary and, often, it must be repeated more than once. This technique involves a superficial incision at about the midpoint of the trabeculate, in the angle opposite the entry point. Trabeculotomy consists of the insertion of a sharp tool in Schlemm's channel (trabeculotomo), which after a rotation towards the anterior chamber, tears the trabeculate, in this way eliminating the resistance to the outflow [21]. Neither technique is free from complication as they can both be associated with hypoema and damages to the crystalline of the iris and ciliary body. The draining implants are prostheses of plastic material which allow communication between the anterior chamber and the space under the capsule of Tenon. They consist of a tube placed in the anterior chamber which is being drained and a filtration plate implanted on the sclera between the extraocular muscles. Some of these implants contain a valve sensitive to pressure to regulate the

outflow of aqueous humor. Many clinical studies have been carried out comparing the patients treated with draining implants to patients treated with other surgical techniques. However, the results do not show significant differences, only that more post-operative dressings are used in the patients treated with draining implants. The complications are: excessive drainage, bad positioning, sclera and conjunctive erosion, obstruction of the pipe by vitreous, blood and iris tissue with following failure to drain and finally, encystment of the swelling [5,18].

Conclusions

Even though the perceived role of IOP in the pathogenesis and diagnosis of glaucoma has changed significantly, lowering IOP levels remains the principal therapeutic instrument in the care and management of sick people. In most cases the first choice option remains medical therapy; however, an accurate evaluation of the individual features of each patient (risk factors, functional state, pressure goal, compliance, tolerability, etc.) is required in order to reach the final aim of the therapy, which is to preserve the visual function of the patient, minimizing the side effects of the treatment and maintaining health and quality of life. The new options in the surgical treatment of glaucoma are considered an improvement (in security and efficiency) of the filtering procedures leading to the development of surgery without swelling. The improvement of classic filtering procedures is surely important through the use of Ex-press, sutures releasable by the sclera door and glues for the closure of the conjunctiva. Instead, surgery without swelling includes procedures which can act both by increasing the outflow of aqueous humor from the anterior chamber and by lowering of the production of aqueous humor. Among the first ones cicloablation could have a new lease on life, not being kept anymore for preterminal cases as a result of the introduction of new techniques. The procedures which increase the outflow from the anterior chamber are more interesting: among them are the procedures which try to restore the outflow from Schlemm's channel (channelplastic [22], I-stent [23], traboctome [24]) and others which divert the aqueous to the suprachoroidal space (y-pass). A very important characteristic of these operations is that they are carried out through a corneal microtunnel, via gonioscopy, drastically lowering the complications and the post-operative recovery. Moreover, thanks to this approach the upper quadrants of the bulbar conjunctiva remain intact, not precluding a possible further filter surgery. Forecasting the future, it is possible to hypothesize an algorithm of surgical treatment, depending on the invasiveness of the treatment itself, which first tries to reactivate the outflow channels by gonioscopy, and secondly, involves the insertion of a shunt suprachoroidal (always by gonioscopy), thirdly, filter surgery, and, finally, a drainage implant in case of failure.

REFERENCES

1. Miglior M, Balacco CG, Balestrazzi E, Bandello F, Boles Carenini B, Bonomi L, Calabria G, Campos E, Cerulli L, Ferreri G, Gandolfo E, Grignolo F, Mastropasqua L, Miglior S, Orzalesi N, Ratig R: I glaucomi ed il sistema dell' idrodinamica oculare: forme cliniche e trattamento. Oftalmologia Clinica, Edit by Monduzzi Editore Oftalmologia, 2006; Cap 16: 409-463.
2. Heiil A, Leske A, Leske MC, Bengtsson B., Hussein M: Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophtalmol 2002; 120:1268-1279.
3. Krieglstein G K, Michelson G: Epidemiologie, Screening, Ökonomie. In: Glaukom 2006, Edit by SpringerLink, Cap 1, 2007.
4. Kanski J J: Oftalmologia Clinica, Edited by Edi Ermes, 2008; Cap 13: 371-440.
5. Dietlein TS, Hermann MM, Jordan JF: The Medical and Surgical Treatment of Glaucoma. Dtsch Arztebl Int 2009; 106:597–606.
6. Nemesure B, Honkanen R, Hennis A, Wu SY, Leske MC, Barbados Eye Studies Group: Incident Open-angle Glaucoma and Intraocular Pressure. Ophthalmology 2007; 114:1810-1815.
7. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophtalmol 2000; 130:429-440.
8. Collaborative Normal-Tension Glaucoma Study Group: The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am j Ophthalmol. 1998; 126:498-505.
9. Lichter PR, Musch DC, Gillespie BW,

Guire KE, Janz NK, Wren PA, Mills RP, CIGTS Study Group: Interim clinical outcomes in the collaborative initial glaucoma treatment study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001; 108:1954-1965.
10. European Glaucoma Society: Terminology and Guidelines for Glaucoma, Edit by Dogma, 2008, 3rd Edition.
11. Singh K, Shrivastava A: Medical management of glaucoma: Principles and practice. Indian J Ophtalmol 2011; 59:88-92.
12. Van der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH: Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophtalmol 2005; 112:1177-1185.
13. Pfeiffer N, Grierson I, Goldsmith H, Appleton P, Hochgesand D, Winkgen A: Fine structural evaluation of the Iris after unilateral treatment with latanoprost in patients undergoing bilateral trabeculectomy (The Mainz II Study). Arch Ophthalmol 2003; 121:23-31.
14. Hylton C, Robin AL: Update on prostaglandin analogs. Curr Opin Ophtalmol 2003; 14: 65-69.
15. McIlraith I, Strasfeld M, Colev G, Hutnik CM: Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. J Glaucoma 2006; 15:124-130.
16. Seah SK, Jap A, Min G: Contact transscleral cyclophotocoagulation for end stage glaucoma. Ann Acad Med Singapore 1994; 23:18-20.
17. Stalmans I, Gillis A, Lafaut AS, Zeyen T: Safe trabeculectomy technique: long term outcome. Br J Ophthalmol 2006; 90:44–47.
18. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL: Treatment outcomes in the tube versus trabeculectomy study after one year of follow-up. Am J Ophtalmol 2007; 143:9-22.
19. Lusthaus JA, Kubay O, Karim R, Wechsler D, Booth F: Primary trabeculectomy with mitomycin C: safety and efficacy at 2 years. Clin Experiment Ophtalmol 2010; 38:831-838.
20. Greenfield DS, Suñer IJ, Miller MP, Kangas TA, Palmberg PF, Flynn HWJr: Endophthalmitis after filtering surgery with mitomycin. Arch Ophtalmol 1996; 114:943-949.
21. Mendicino ME, Lynch MG, Drack A, Beck AD, Harbin T, Pollard Z, Vela MA, Lynn MJ: Long-term surgical and visual outcomes in primary congenital glaucoma: 360 degrees trabeculotomy versus goniotomy. J AAPOS 2000; 4:205-210.
22. Matthaei M, Steinberg J, Wiermann A, Richard G, Klemm M: Canaloplasty : A new alternative in non-penetrating glaucoma surgery. Ophtalmologe 2010; 12:1169-1175.
23. Nichamin LD: Glaukos iStent® trabecular micro-bypass. MEA J Ophtalmol 2009; 16: 138-140.
24. Gunderson E: Trabeculotomy Ab Interno, using the Trabectome: a promising treatment for patients with open-angle glaucoma. Insight 2008; 33:13-15.