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Use of antiglaucomatous drugs in patients with severe glaucoma: how many are necessary to control the disease?

Uso de drogas antiglaucomatosas em pacientes com glaucoma severo: quantas são necessárias para controle da doença?

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ABSTRACT

Introduction: *Glaucoma is the main cause of irreversible blindness in Brazil. To date, there is no ideal drug for the control of intraocular pressure (IOP), usually requiring the combination of two or more hypotensive drugs, with frequent daily instillations and poor adherence to treatment.* ***Objectives:*** *To describe quantitatively and qualitatively the drugs used to control IOP and the efficacy of treatment in the prevention of blindness.* ***Methods:*** *A retrospective cross-sectional study was carried out through a review of 420 medical records of patients with severe Glaucoma who were followed up at the Emílio Carlos Hospital outpatient clinic in Catanduva, SP, from January 2014 to December 2016. The analyzed variables were: age, visual acuity and antiglaucomatous drugs used: topical (eye drops) and systemic.* ***Results:*** *The mean age of participants was 62.99 ± 16.29 years. Sixty-eight cases of blindness were detected, and three patients (0.7%) lost vision at the time investigated, with references to periods without treatment / subdose / improper instillation / use of 3 or 4 eye drops. In 73.3% of the cases, IOP stabilization was achieved with one (38.1%) or at most 02 (35.2%) associated drops. There was a significant correlation between the number of combinations of topical hypotensive agents and the number of patients taking acetazolamide. The drugmostused was Timolol (67.1%).* ***Conclusions:*** *In the majority of patients IOP was controlled with 1 or 2 associated eye drops; small percentage of cases evolved into blindness; most likely the evolution to loss of vision was due to the complexity and poor adherence to the treatment.*

Keywords: *Glaucoma; Intraocular pressure/drug therapy;Blindness/prevention & control*

RESUMO

Introdução: O glaucoma é a principal causa de cegueira irreversível no Brasil. Até o momento não se dispõe de uma droga ideal para o controle da pressão intraocular (PIO), geralmente necessitando associar dois ou mais medicamentos hipotensores, com frequentes instilações diárias e má aderência ao tratamento. **Objetivos:** Descrever quantitativa e qualitativamente as drogas usadas para controle da PIO e a eficácia do tratamento na prevenção da cegueira. **Métodos:** Estudo transversal retrospectivo, através de revisão de 420 prontuários de portadores de Glaucoma severo acompanhados no ambulatório do Hospital Emílio Carlos, de Catanduva-SP, de janeiro/2014 a dezembro/2016. As variáveis analisadas foram: idade, acuidade visual e medicamentos antiglaucomatosos utilizados: tópicos (colírios) e sistêmicos. **Resultados:** A média de idade dos participantes foi 62,99±16,29 anos. Foram detectados 68 casos de cegueira, sendo que 3 pacientes (0,7%)perderam a visão no tempo investigado, com referências a períodos sem tratamento/subdose/instilação indevida/uso de 3 ou 4 colírios. Em 73,3% dos casos conseguiu-se estabilização da PIO com o uso de um (38,1%) ou no máximo 02 (35,2%) colírios associados. Houve correlação significativa entre o nº de combinações de hipotensores tópicos e o nº de pacientes em uso de Acetazolamida. O medicamentomais usado foi o Maleato de Timolol (67,1%). **Conclusões:** Na maioria dos pacientes a PIO foi controlada com 1 ou 2 colírios associados; pequena porcentagem dos casos evoluiu para cegueira; muito provavelmente a evolução para perda de visão foi decorrente da complexidade e má aderência ao tratamento.

Descritores: Glaucoma; Pressão intraocular/tratamento farmacológico; Cegueira/prevenção& controle

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Introduction

Glaucoma is the leading cause of irreversible blindness in Brazil[1] and the world.[2] It is an optic neuropathy with asymptomatic, chronic, hereditary, bilateral and asymmetric multifactorial etiology, with three main elements in its diagnosis: characteristic optical disc excavation, increased intraocular pressure (IOP), and progressive loss of visual field. Early diagnosis aims at appropriate IOP control for the maintenance of the optic nerve integrity. Many patients need the association of two or more hypotensive drugs for this control to be effective. [3]

However, an ideal drug to control glaucoma is not yet available, that one that can be used in all types of glaucoma and in all patients to stop the progression of glaucomatous damage. In many patients, the association of two or more hypotensive drugs is necessary for the control of IOP to be effective.[3] To overcome this, there are currently pharmacological groups of ocular hypotensors, each of which with numerous commercial products which often only give profit to the pharmaceutical companies. It is true that drugs are combined to increase their hypotensive effect, and that they are used as vehicles to produce a longer effect, thus reducing the frequency of use, among others. However, it is well known that different products come to the market with the same active principle and different cost, causing a dilemma for the ophthalmologist and the patient. [4-6]

Patients with advanced functional loss or young patients with established disease should have a more aggressive treatment and a closer follow-up than patients at lower risk, such as patients with only increased IOP without optic disc alterations or visual field impairment or other changes.[7-8]

It should also be considered that individuals with ocular hypertension and primary open-angle glaucoma who use eyedrops daily are more likely to have damages on the ocular surface with varying signs and symptoms, including changes of the conjunctival bacterial flora, when compared to the normal population. [9-12] It is known that both the active principle of topic ocular hypotensive agents (eyedrops) and the preservative used, usually benzalkonium chloride (BAK), can cause and/or worsen the changes in the ocular surface. [9,13]

The Brazilian public health system provides anti-glaucomatous drugs according to the high cost program.[14,15] The goal of glaucoma treatment is to improve the patient's quality of life by maintaining vision with minimal adverse effects. Knowledge of resource utilization costs and treatment standards for glaucoma patients is an important condition for assessing the impact of its increased prevalence on health budget. [1] In view of the relevance of the subject, the present study aimed to describe quantitatively and qualitatively the antiglaucomatous drugs used to control IOP and the efficacy of the treatment in the prevention of blindness.

Methods

A retrospective cross-sectional study in which the medical records of 943 patients with disease classified by ICD-10 were reviewed using the code H40.9 (Glaucoma), listed by Centro de Processamento de Dados do Hospital Padre Albino, Catanduva-SP, and followed at the Glaucoma ambulatory of Hospital Emílio Carlos (HEC), in the same city, from January 2014 to December 2016. Of this review, only 420 cases complied with the criteria for diagnosis of Severe Glaucoma (optic disc excavation greater than 0.75), and thus the remaining 523 cases were excluded from the study. Patients followed at said service were treated according to the protocol of the service, and all treatment data was recorded in the medical record. The frequency of follow-up visits was based on the severity of each case.

The data collected was stored in a Microsoft Office Excele spreadsheet, and the variables analyzed were age, origin, visual acuity, antiglaucomatous drugs used (topic/eyedrops and systemic), and previous surgeries.

The results were expressed in number, percentage, average and standard deviation (in the case of age). The Z test for Two Proportions was used to compare the variables. $P \leq 0.05$ was considered significant.

The present study was approved by the Research Ethics Committee/FIPA under the opinion No. 2.060.314 and CAAE No. 67665417.7.0000.5430, and the signature of the Free and Informed Consent Term because was considered unnecessary as it was a study of medical records.

Results

The average age of the 420 participants was 62.99 ± 16.29 years (8 to 93 years).

Regarding the origin of the patients, only 63 (15%) resided in Catanduva, with the rest coming from the microregion comprising 18 neighboring municipalities located within a radius of 170 km.

The distribution of patients according to the visual response profile is shown in Table 1, where it is observed that 3 (0.7%) patients lost sight during the time of investigation. In the records of these 3 cases there were references to the use of 3 or 4 eyedrops associated and failures in the use of the prescribed medication (periods without treatment, doses lower than those recommended and inadequate instillation).

The average age of blindness in both eyes was 66.2 ± 12.7; blindness in the left eye 67.3 ± 17.6; blindness in the right eye 70.3 ± 16.4.

Figure 1 shows the distribution of participants according to the pharmacological group of the topic hypotensives used, and figure 2 according to the presentations of these hypotensives available in the high cost program. [14,15]

The amount of hypotensive drugs used to control IOP is shown in figure 3. It was observed that 73.3% of the individuals studied achieved IOP control with the use of one or at most 2 associated eyedrops, and that there was a correlation between the number of combinations of topic hypotensive agents -HT (1, 2, 3 and 4) and the number of patients taking acetazolamide (0.6%, 2.1%, 11.3% and 50%, respectively), with a statistical significance of $p<0.001$.

Table 1
Distribution of patients with severe glaucoma followed at the ambulatory of HEC, Catanduva-SP, from January 2014 to December 2016, according to the visual response profile

Ambulatory follow-up*	Blindness† **	n (%)
First appointment	65	(15.5)
Last appointment	68	(16.2)

*420 cases of severe glaucoma; **One or both eyes.

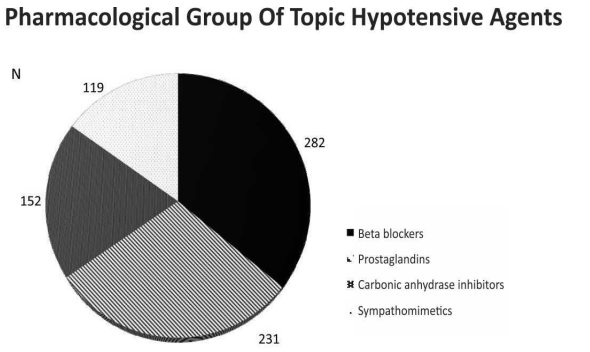

Figure 1: Distribution of patients with severe glaucoma followed at the ambulatory of HEC, Catanduva-SP, from January 2014 to December 2016, according to pharmacological group of topic hypotensive agents used.

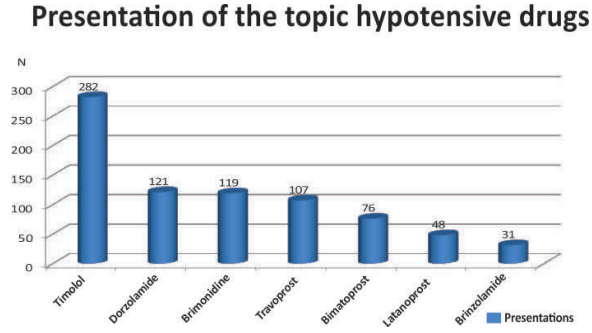

Figure 2: Distribution of the 420 patients with severe glaucoma followed at the ambulatory of HEC, Catanduva-SP, from January 2014 to December 2016, according to the presentations of topic hypotensives available in the high-cost program.

Regarding the record of ophthalmologic surgeries, 3 (0.7%) patients had undergone iridectomy and 2 (0.5%) had trabeculotomy.

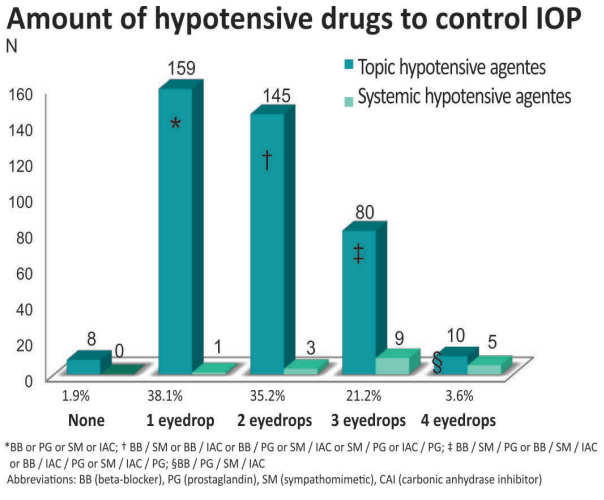

Figure 3: Distribution of the 420 patients with severe glaucoma followed at the ambulatory of HEC, Catanduva-SP, from January 2014 to December 2016, according to the amount of hypotensive drugs used to control IOP. .

Discussion

Treatment of primary open-angle glaucoma, as far as possible, should initially be clinical. Its purpose is to promote stabilization, and delay or prevent the appearance of glaucomatous changes by reducing the IOP. [16]

The main point is the timing of initiating treatment in patients with ocular hypertension. It is a consensus to start therapy in the case of IOP above 26 mm Hg in thinner or normal-thickness corneas when the anatomical and functional monitoring cannot be performed satisfactorily. In cases with a risk factor, the decision must be specific to each patient. [16]

The choice of ocular hypotensive agent depends on factors related to the particularities of each patient (concomitant diseases, social condition), and also the characteristics of the action of each antiglaucomatous agent and its side effects. In addition, it is important to develop a good doctor-patient relationship, since the main cause of therapeutic failure is due to the low fidelity to the clinical treatment, and not due to the inefficacy of the drugs used. [16]

It is recommended to start treatment with topic monotherapy in order to reach the target IOP. The choice for the initial drug should be individualized, but classically clinical treatment starts with a topical beta blocker (Timolol Maleate, Levobunolol Hydrochloride, Betaxolol Hydrochloride, and Metipranol Hydrochloride) or, if socioeconomic conditions allow, a prostaglandin (Latanoprost , Bimatoprost, Travoprost and Isopropyl Unoprost). [16]

The effectiveness of the treatment should be evaluated in a variable time and according to the drug used, observing the IOP level, the risk factors of the patient, and the stage of the disease. When the target IOP is reached, control appointments are recommended. In cases where the target IOP can not be achieved, the decision to replace or associate another hypotensive agent will depend on the magnitude of the IOP reduction. It is recommended to replace or associate another hypotensor when the initial IOP reduction is greater than 10%. If the reduction is less than 10%, there is a consensus on replacing the initial medication. [16]

Antiglaucomatous drug combinations should follow some basic rules, such as: not associating drugs from the same pharmacological group; avoiding the use of substances of the same pharmacological group by different routes of administration (topical and systemic); considering the number of instillations required by the association prescribed, and always carefully considering the impact on the quality of life of the patient in all aspects (professional, social, economic, etc.). [16]

Other drugs available in Brazil to assist in the treatment of glaucoma are: (Brimonidine, Brimonidine tartrate and Brimonidine), Carbonic anhydrase inhibitors (Dorzolamide, Trusopt, Brinzolamide and Acetazolamide) and parasympathomimetic (Pilocarpine). [16]

According to Sociedade Brasileira de Glaucoma (SBG) [16], the choice of medication to start treatment of this disease should be customized, but it is usually chosen by the use of only a topical hypotensive, being a beta-blocker or a prostaglandin.

As shown in figure 1, the participants of the present study used, with the exception of the parasympathomimetics, at least 1 of the drugs of each pharmacological group indicated by the SBG to treat Glaucoma Glaucoma16, and the majority of them (67.1%) made use of the Beta Blocker (Figure 2).

The analysis of the amount of hypotensive drugs required to control IOP (Figure 3) showed that in most cases (73.3%) IOP stabilization was achieved using only one (38.1%) or at

most 02 (35.2%) topic hypotensive agents (HT) associated. A study developed in an Ophthalmology Department of Hospital de São José do Rio Preto - SP along with a Reference Center in Ophthalmology of a Federal University of Goiás aimed at evaluating the hypotensive efficacy and adversities of Bimatoprost replacing the Latanoprost/Timolol or Dorzolamide/Timolol in the treatment of glaucoma concluded that the treatment with Bimatoprost resulted in a significant reduction of the IOP when compared to Dorzolamide/Timolol and Latanoprost/Timolol combinations. [17]

In the current research, the most used drug at the time of onset of treatment (Figure 2) was a topical beta blocker, rather than the most costly prostaglandins. This finding can be justified by the fact that all study participants were users of the Brazilian Single Health System (SUS), and although the recommended medications are part of the Assistance Program for Glaucoma Patients [14,15] it is well known that the logistics for this benefit is very complex and time-consuming. Literature review[4] reports that in Cuba timolol use is preferred mainly because of its greater availability and lower cost, and for having demonstrated over time its safety and efficacy, despite a lower hypotensive effect.

Our study found that acetazolamide (systemic hypotensive) was used in 4.3% of patients in combination with topic hypotensive drugs. This drug acts by inhibiting the enzyme carbonic anhydrase (CA) and preventing the reabsorption of HCO3- in the proximal contorted tubule, leading to osmotic diuresis as a systemic effect. In glaucoma, its action is due to the decrease in the production of aqueous humor and, consequently, reduction of the IOP. [18] It effectively decreases the IOP during the day, with less effect at night. However, for this mechanism to be effective, inhibition of at least 90% of the CA enzyme is necessary.[19] According to Wang et al. , [20] CA inhibitors are associated to an IOP decrease of 18-22%, and may be used in monotherapy or more frequently in combination with α2 adrenergic agonists or β adrenergic blockers. As shown in figure 3, the use of the systemic hypotensive agent (acetazolamide) was significantly correlated with HT use, i.e., the greater the number of combinations of topic hypotensive agents (01, 02, 03 and 04 associations), the greater the use of the systemic drug (0.6%, 2.1%, 11.3% and 50%, respectively). This fact may be explained by the systemic medication being usually recommended as an adjunct to control the IOP in association with topical medication. [20]

In order for the treatment of glaucoma to be successful, some factors need to be considered, among them the patient's commitment to the therapy proposed (adhesion).[21] The complexity of a therapeutic regimen (number of drugs and frequency of instillations) may be associated to a decrease in adherence of treatment for glaucoma.[22-24] A recent publication[25] shows the lack of uniformity of the drops released by commercially available eyedrops and their inadequacy to the real need, since the drops released are larger than indicated, which becomes a problem when used for prolonged treatment. One can estimate the impact on the patient's life taking into account that an interval is needed in the use of eyedrops, and that some of them should be used 2 or more times a day.[26] A consistent alternative is the prescription of a single drug with a single daily dose,[27] with hypotensive efficacy and tolerability similar to or greater than two or more associations. [28] Another preponderant aspect for the success of the therapy is to advise the patient on the proper use of the topic medication, especially with regard to correct instillation of eyedrops.[16] Aside from this, the financial value of the treatment should also be considered, since coverage for patients with glaucoma in the public health system does not reach the entire population and the cost of topic hypotensive agents can represent up to 30% of the minimum wage. [26]

The follow up of the records of each participant of this research showed that 3 patients (0.7%) lost sight during the time of study. In the records of these 3 cases there were references to the use of 3 or 4 eyedrops associated and failures in the use of the prescribed medication (periods without treatment, doses lower than those recommended and inadequate instillation). Although the number of individuals who progressed to blindness has been restricted, these findings suggest that the complexity and poor adherence to treatment may have been the cause of ineffective IOP control and consequent loss of sight.

Except for the clinical treatment already mentioned, 1.2% of participants in our study underwent surgical treatment to control Glaucoma. One of the procedures performed was the trabeculectomy, which is a modality of antiglaucomatous surgery in which an alternative pathway is created to the flow of the aqueous humor into the systemic circulation, allowing its absorption by the subconjunctival blood vessels, aqueous veins and lymphatic vessels.[29] It is recommended for patients with uncontrolled IOP due to the inefficiency of the hypotensive drugs used or the lack of clinical or socioeconomic conditions for the use of the medications, or for those in need to delay the surgery provided they do not have advanced glaucoma and/or are young. The initial IOP can be reduced up to 30%, with a loss of effectiveness of approximately 10% per year. It is not a good option when there is a need for expressive reduction of IOP, and it is not usually effective in young patients. [16] In our investigation, only 0.5% of patients underwent this surgical procedure: one of them, 30 years old, who used the hypotensive bromonidine; and the other, 63 years, with loss of sight in the left eye, using timolol, bromonidine, brinzolamide and acetazolamide.

Another surgical procedure performed in the participants of this investigation was the iridotomy/laser iridectomy, which consists onthe creation of a pertuit to communicate the anterior chamber with the posterior chamber aiming to equalize the pressure difference between the two chambers and relieve the relative pupillary block. Its main indications are prophylaxis of acute glaucoma in patients with occlusible angle; immediately after the clinical resolution of an acute glaucoma crisis; in the cases of chronic closed-angle primary glaucoma to eliminate the relative pupillary block and the formation of goniosynequias; and in patients with pigmentary dispersal syndrome and pigmentary glaucoma to eliminate reverse pupillary block.[29] In the research in question, 3(0.7%) patients underwent this surgery: a 74-year old one using brinzolamide, bromonidine, bimatoprost and acetazolamide; another 75-year old one using timolol, dorzolamide and travoprost; and the last one, 65 years old, with loss of sight in the left eye and using detimolol, bromonidine, travoprostaeacetazolamide.

Although limited in scope due to the limited casuistry, the results discussed above helped to understand the factors involved in the treatment of the population attended in the glaucoma ambulatory of HEC in Catanduva-SP, and suggest the need to provide detailed patient guidance and frequent follow-up of the treatment, in order to minimize greater damages, that is, the irreversible loss of sight.

Conclusion

The present study allowed us to conclude that 3/4 of the patients managed to control IOP with the use of one or at most two eyedrops associated. A small percentage of cases evolved to blindness, and the development to loss of sight was most likely due to the complexity and poor adherence to the treatment. This conclusion suggests the need for more rigorous supervision of the treatment of this serious disease, which can be done through the involvement of family members and the multidisciplinary team of the public health units of their municipalities, since they are all SUS users and, in the majority, residents of neighboring cities.

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