GENERAL REVIEW

CURRENTS ON TARGET INTRAOCULAR PRESSURE AND INTRAOCULAR PRESSURE FLUCTUATIONS IN GLAUCOMA MANAGEMENT

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ABSTRACT

Over the past decade, results from prospective, randomized, clinical trials have confirmed the value of reducing intraocular pressure (IOP) in patients with ocular hypertension or primary open-angle glaucoma and have outlined the need to consider a target IOP in an individual glaucomatous patient and not an arbitrary value of 21 mm Hg as classically believed. The target IOP corresponds to an estimation of the mean IOP obtained with treatment that is expected to prevent further glaucomatous damage. Target IOP is difficult to assess accurately in advance in every individual patient and eye. Moreover, no degree of IOP is proven to be safe for every patient. This paper will deal with the criteria that can be used to approach as closely as possible and periodically re-assess the range of the target IOP in an individual.

Although IOP has been found to be more variable in glaucomatous than in healthy eyes, the potential role of diurnal IOP fluctuations in the development or progression of glaucomatous damage is still unclear. It has been strongly suggested in a recent past that abnormal 24-hour IOP fluctuation could be a significant risk factor for glaucomatous damage. There is still currently insufficient evidence to support that both 24-hour IOP fluctuation and IOP variation over periods longer than 24 hours are an independent and separate risk factor for glaucomatous damage. Until further confirmation on their exact role in glaucoma development and progression, the goal of detecting and reducing abnormal 24-hour IOP fluctuation is warranted in all newly diagnosed glaucomatous patients as well as in patients who continue to progress at lower pressures.

RESUME

Les essais cliniques prospectifs, randomisés qui ont été réalisés au cours de ces dix dernières années, ont permis de confirmer l'effet bénéfique de la réduction de la pression intraoculaire (PIO) sur l'apparition et/ou l'évolution du glaucome et ont souligné la nécessité de prendre en considération une PIO cible chez tout patient glaucomateux au niveau individuel au lieu de la valeur arbitraire et quelque peu "magique" de 21 mmHg comme c'était le cas depuis de très nombreuses années. La PIO cible représente une estimation de la PIO moyenne qu'il convient d'obtenir par le traitement et qui devrait permettre de prévenir l'aggravation des déficits glaucomateux. La valeur de la PIO cible est difficile à apprécier à l'avance de manière précise au niveau individuel, que l'on considère le patient ou l'œil du patient. De plus, il n'existe pas de niveau de PIO qui soit vraiment sûr pour un patient donné. Cet article se focalisera sur les critères qu'i convient de respecter pour approcher la valeur de la PIO cible aussi précisément que possible et la réévaluer périodiquement au niveau individuel.

Bien qu'il ait été montré que la PIO était sujette à de plus grandes variations chez un patient glauco-

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mateux que chez un sujet sain, le rôle exact des fluctuations diurnes de la PIO sur le développement ou la progression des déficits glaucomateux reste imprécis. Il a été récemment suggéré qu'une fluctuation diurne anormale de la PIO pouvait être un facteur de risque significatif pour le développement et l'aggravation des dommages glaucomateux. Toutefois, on ne dispose pas encore d'arguments suffisamment tangibles pour conclure qu'aussi bien une fluctuation anormale de la PIO sur 24 heures que sur un plus long terme, représente un facteur de risque indépendant et séparé pour le glaucome. Jusqu'à plus ample confirmation toutefois, la détection et la réduction thérapeutique des éventuelles fluctuations anormales de la PIO se doit d'être un objectif prioritaire chez tout patient glaucomateux nouvellement diagnostiqué, de même que chez les patients qui continuent à s'aggraver en dépit d'une réduction très substantielle de leur PIO et d'une observance thérapeutique apparemment correcte.

KEYWORDS

Intraocular pressure, ocular hypertension, glaucoma, target pressure, intraocular pressure fluctuation, Quality of Life, treatment.

MOTS-CLES

Pression intraoculaire, hypertension oculaire, glaucome, pression cible, fluctuations de la pression intraoculaire, qualité de vie, traitement.

Glaucoma is a progressive optic neuropathy associated with characteristic optic nerve findings, visual field loss and various risk factors including intraocular pressure (IOP) (46). The results of prospective randomized clinical trials (RCT's) have shown that the vast majority of glaucoma damage is pressure dependent and might therefore be preventable. These studies have confirmed the value of intraocular pressure (IOP) reduction to retard the progression of glaucomatous optic nerve damage in early as in late disease as well as both at normal and high IOP levels (9, 18, 24,29,30, 32, 33). RCT's have also outlined the need to consider a target IOP in an individual glaucomatous patient and not an arbitrary and somewhat "magic" value of 21 mmHg as suggested for a long time. However questions about the validity of considering the related issue of diurnal and 24-hour IOP fluctuation as a separate and independent risk factor for glaucomatous damage are still unanswered.

The aim of this review is to take stock of these two relatively new concepts of Target IOP and IOP fluctuations, which have noticeably changed our management of glaucomatous patients in the last few years.

TARGET IOP

Background

Glaucomatous patients are at risk of developing damage to their vision, which may alter their quality of life. The goal of treatment is to maintain patient's overall Quality of Life (QoL) by balancing the respective risks of treatment and disease (22, 32, 40).

Patient's risk of developing and progressing glaucomatous damage is related to IOP (9,18,42,45). Lowering the IOP is until now the only available option to treat glaucoma patients. By lowering IOP, one aims at bending the curve of glaucomatous ganglion cell loss towards the curve of loss by aging and at reducing the rate of progression of glaucomatous damage (22,49). The degree to which the IOP should be reduced to reach this goal is still unfortunately unknown.

Given that the rate of progression of glaucomatous damage is different for each patient, glau-

coma patients should not be thought of as being stable or progressing but rather as progressing at varying rates. Rates of glaucoma progression are often non linear. Many patients progress in spite of a significant reduction of their IOP. Patients who appear to be stable, based upon visual field and optic disc evaluation, may suddenly worsen, even without a significant IOP change (44). Similarly, patients, especially those suffering from advanced glaucoma, may continue to further progress after having lowered their IOP in the low teens. It has been suggested that some patients may have an IOP-independent component for damage (7)
Although it is well-known that the lowest possible IOP will be the safest for preventing further glaucomatous damage, it should also be considered that very low IOPs may have drawbacks and that medications needed to reach this level have potential side effects (49).
Indeed, well known risk factors other than IOP may influence a patient's risk of developing and/or worsening glaucomatous damage (age, optic nerve and visual field status, heredity, central corneal thickness, high myopia, systemic hypertension, systemic hypotension, vasospastic disorders, and so on..) and should be addressed whenever possible.
The concept of a target IOP recognizes that IOP reduction may be used as "a surrogate for the real goal of maintaining each patient's overall QOL to the greatest extent possible" (22). Ideally the patient should be a partner in the decision of the target IOP value to obtain. In any case, it should be kept in mind that there is no single IOP level that is safe for every patient. Some patients will continue to progress despite apparent achievement of their target IOP and vice versa. The concept of target IOP does not imply that all patients with borderline or elevated IOP should be treated (22). In addition, the exact baseline IOP is often unknown and therefore the target IOP can only be estimated.

Assessment of target IOP in clinical practice

There are currently neither consensus on the exact definition of target IOP which may vary for each physician and each patient nor agreement with the exact benefits of a variable target IOP on the evolution of glaucomatous disease itself (7,22). According to the EGS Guidelines, the target IOP is ''an estimate of the mean IOP obtained with treatment that is expected to prevent further glaucomatous damage'' (41). Owing to the fact that we cannot halt glaucoma, but only reduce the rate of progression, there is an alternate definition which considers that the target IOP is "an estimate (i.e a range of IOP's) of the mean IOP at which the risk of decreased vision-related QoL due to glaucoma exceeds the risk of treatment" (22).

The target IOP determination is based on an individual glaucoma risk assessment (22,41). This includes

1. *The estimation of the amount of glaucoma damage* based upon optic disc and visual field assessment. The more severe the damage at the time of diagnosis, the lower the target IOP should be. The lower is the initial IOP, the lower will be the target IOP and vice versa.
2. *The appreciation of the damaging IOP*, i.e the "maximum" IOP at which damage has presumably occurred. Multiple IOP measurements at different times of the day should be recorded to appreciate the exact damaging IOP.
3. *An anticipation of the patient's life expectancy*. Logically, the longer the patient's longevity, the lower the target IOP will need to be.
4. *The identification of the other risk factors for progression,* such as the presence of a severe damage in the other eye, family history of blindness from glaucoma, high myopia, ethnicity, vascular risk factors, and so on...
5. *The assessment of the rate of progression of glaucoma damage*, i.e the severity of damage that has already occurred versus time. In other words, what is the likelihood that a patient will reach visual disability given his/her rate of visual field and/or optic disc progression.

Once these 5 steps are complete, the closest possible approach to the exact target IOP should be chosen. The use of a percentage of reduction has the disadvantage to discard the risk of further damage. So, in the OHTS, a target IOP lowering of at least 20% below baseline was

Table 1: *Recommended target IOPs in the Guidelines of the European Glaucoma Society (2003)*

Target IOP in POAG	
Early glaucoma (MD < 6 dB)	<18 mm Hg
Moderate glaucoma (MD ⩽ 12 dB)	<15 mm Hg
Advanced glaucoma (MD > 12 dB)	< 12 mm Hg
Terminal glaucoma	< 10 mm Hg
Target IOP in NTG	
Early glaucoma (MD < 6 dB)	<15 mm Hg
Moderate glaucoma (MD ⩽ 12 dB)	<12 mmHg
Advanced glaucoma (MD >12 dB)	< 10 mm Hg

required in the treatment group (24). The EMGT aimed at obtaining a 25% reduction (18). The AGIS and CINTG have recommended to adopt target pressures in the low teens corresponding to a 35% or more IOP reduction for patients with advanced primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG) (9,42).

Additional risk factors (e.g family history, rates of progression, myopia, and vascular factors) are not included in most of the available formulas. Moreover, many formulas cannot be applied in a linear way and may therefore be less suitable in extreme conditions, such as very high baseline IOPs. An interesting algorithm is a variation of the formula proposed by T. Zeyen , i.e "Target IOP= Maximum IOP - Maximum IOP % - Z", where Z corresponds to the optic nerve damage severity factor ranging from 0 to 3: grade 0 corresponds to a normal disc and a normal visual (VF) field, grade 1 to a glaucomatous optic disc but a still normal visual field in automated perimetry, a grade 2 to a VF loss that does not threaten fixation and grade 3 to a VF loss threatening or involving fixation (21,49).

For example, an eye with a maximum IOP of 25 mmHg, optic nerve damage and visual field loss threatening the fixation would have a initial target set at 16 mm Hg (25 - 25% - 3).

The EGS Guidelines have the great advantage to give a general, simple and practical directive (41). So, in POAG, the target IOP will be lower than 18 mmHg in early glaucoma, lower than 15 mmHg in moderate damage, lower than 12 mmHg in advanced disease and less than 10 mmHg in terminal glaucoma.

Indeed, these values should be further reduced in patients with NTG from about 2 to 3 mmHg.

Table 1 summarizes the target IOP recommended by the EGS in POAG and NTG respectively.

If one uses a target IOP, or better a target IOP range, as a guide to glaucoma management, it needs to be recorded and highlighted in the chart of the patient. This represents a reminder of the previously estimated ideal IOP range at each follow-up visit (22).

Importantly, the use of a target IOP in glaucoma needs periodic re-assessment (22). This is based on the detection of the presence or not of glaucomatous progression, the effect of the treatment on the patient's QoL and the presence of a systemic illness that might affect the risk/benefit ratio or therapy or could significantly shorten life expectancy. As the patient is periodically monitored, it will be concluded at each visit that either the target is appropriate or must be lowered or, on the contrary, it can be raised.

Exclusion of other risk factors, such as systemic hypotension, poor compliance or IOP spikes is warranted at each visit.

Whenever the target IOP is changed, the date of the change and the new target IOP should also be recorded in the chart of the patient (22).

Clinical messages

- Target IOP is an IOP range that is considered unlikely to cause further glaucomatous damage. The target IOP is derived from a risk factor analysis of outcomes for individual patients.
- The level to which the IOP should be lowered is different for each individual patient.
- An initial target IOP is only a temporary guess.
- Because there is no validated algorithm for its calculation, target IOP cannot be deter-

mined with any certainty in an individual patient.
- The target IOP should be recorded so that it is accessible on subsequent patient's visits, and it requires periodic re-assessment.

IOP FLUCTUATIONS: MYTH OR REALITY?

One of the current topics in glaucoma research is to determine which aspect of IOP is the most important in glaucoma development or progression. Questions regarding whether we are most concerned about the mean IOP over time, the IOP fluctuations over time or peak pressures over a safe level is still debated. In other words, there is until now a lack of evidence for assessing that IOP fluctuation is a separate and independent risk factor for glaucoma (32,37).

Characteristics of IOP fluctuation

The reliability of the assessment of the exact IOP fluctuation can be altered by numerous and complex factors,
- In addition to the imprecision of IOP measurements themselves, methods and feasibility of IOP measurements can differ (used instruments, measurements obtained at home, in office or in clinic by ophthalmologists, residents or nurses,..).
- IOP measurements have been proven to be variably dependent on the physical properties of the cornea (5,26).
- IOP measurements only reflect the IOP at a single time point.
- The terminology of IOP fluctuation is still confusing. Whether IOP fluctuation should be assessed over hours, days, weeks or over the long term or whether it corresponds to the peak, to the range or to the standard deviation of the IOP measurements is still unclear (37).
- Finally the treatment effect, the compliance with treatment, the frequency of IOP measurements and the difficulty of assessing true progression represent potentially confounding variables in the determination of the true IOP fluctuation (18).

IOP fluctuations can be divided into three types: 1.Ultrashort-term fluctuations which occur in minutes, such as those due to a Valsalva maneuver during measurement, 2. short-term fluctuations that can occur over hours or days which in turn can be subdivided into daytime and nocturnal variations and 3. long-term fluctuations that occur over months or years (1,32).

Similarly to other biological rhythmic cycles, IOP varies periodically on a 24-hour period. Circadian IOP fluctuations occur both in healthy individuals and glaucomatous eyes. IOP variations reflect physiological circadian and environmental factors, abnormal regulation of IOP due to the aqueous inflow/outflow system disease, or a combination of these factors (12,32,35).

The physiological range of daily IOP fluctuation is believed to be more or less than 5 mmHg (32).

In normal eyes, IOP is generally elevated overnight and in the early morning and decreases during the day. By contrast, glaucomatous eyes exhibit a reverse curve compared to normal subjects with a mean diurnal IOP that is higher than the mean nocturnal IOP and a predominance of morning or mid-day IOP maxima (43). This suggests that the regulation of IOP in glaucomatous eyes could be different from the normals. During the diurnal period, IOP fluctuates more in glaucomatous patients than in normals. 24-hour fluctuations of 8 to 10 mmHg have potentially deleterious effects on the optic nerve fibres.

Due to these chronobiological characteristics, the diurnal period could be considered as the more relevant to be studied (32).

Long-term IOP variations are generally appreciated at various daytime hours during multiple office visits and may reflect normal aging as well as the disease process itself (32).

Recent papers had outlined the importance of supine IOP, especially nocturnal/sleep period IOP (8,15,25,47). IOP is lower in the sitting position than in the supine position both in normal and glaucomatous eyes secondary to the elevation of the venous episcleral pressure in the supine position. The diurnal IOP variation in the sitting as well as in the supine position has been found to be larger in glaucomatous eyes compared to normal eyes. By contrast, during the nocturnal period, variations of supine IOP would not be different between normal and glaucomatous eyes (31).

IOP has also been found to be the lowest during Rapid Eye Movement (REM) sleep and highest during slow wave sleep periods. Upon awaking, the IOP rises both in normal and glaucomatous eyes compared to the pre-sleep values and returns to baseline levels over about 10 minutes (6,48).

At the present time, there is no optimal tool to continuously monitor IOP fluctuations in a real time situation. 24-hour IOP measurements are practically very difficult to perform. The methods for studying 24-hour fluctuations include hospitalization which potentially alters the normal activity of the patient. Multiple office hour measurements only assess a portion of the 24-hour IOP. It has been found to be probably unable to correctly identify IOP peaks in contrast to 24-hour IOP measurements (2,20,34). Moreover there is currently no valid and simple way to continuously check IOP during sleep since measuring IOP needs waking the patient up. The use of a contact lens has been recently proposed to monitor 24 hour IOP by telemedicine in the future (Pitchon EM. Et al. ARVO 2008 abstract 687/D960).

IOP may also differ according to the type of glaucoma. IOP tends to vary most in angle closure glaucoma due to intermittent closure of the angle, and in secondary open-angle glaucomas such as pigmentary glaucomas and pseudoexfoliation syndromes (32).

Short-term IOP fluctuation as a glaucoma risk factor

Some authors have suggested that short-term fluctuation could be a risk factor for glaucoma. Based on self-tonometry performed at home during five consecutive days in glaucoma patients with office IOP in the normal range, Asrani et al concluded that large diurnal IOP fluctuations are a significant risk factor for visual field progression independent of the IOP level (1). This report has often been cited as a proof for variability as a risk factor for glaucoma progression. Similarly Collaer et al have found that there was a significant relationship between visual field deterioration and the IOP range and peaks in patients with NTG (10). However Liu et al performed IOP measurements at a sleep lab every two hours over the 24-hour period both in untreated newly diagnosed glaucoma patients and age-matched healthy subjects and found that the mean diurnal IOP was higher in the glaucoma eyes, but that the diurnal to nocturnal IOP range was larger in the healthy eyes. Therefore their study failed to support the notion that a large 24-hour IOP variation is associated with early glaucomatous changes (31).

Long-term IOP fluctuation

The literature addressing the relationship between long-term IOP variation and progression of glaucoma has also given conflicting results.

In a *post-hoc* multivariate analysis of the AGIS data in which long-term IOP variation was calculated as the standard deviation of all single measurements recorded at different days during the follow-up after the initial surgery, Nouri-Mahdavi et al found that long-term fluctuation remained a strong predictor factor for visual field deterioration despite the inclusion of mean IOP and number of surgeries as independent variables in the models (36). They found that eyes with an IOP SD < 3 mm Hg remained stable over time, whereas eyes with an IOP SD $\geqslant$ 3 mm Hg demonstrated significant progression. Conclusions of the Collaborative Initial Glaucoma Treatment Study (CIGTS) and of other studies were similar (19,30).

In contrast to these findings, the Early Manifest Glaucoma Trial (EMGT), as well as the European Glaucoma Prevention Study did not find any correlation between long-term IOP variation and the risk of glaucoma progression and development respectively, and found no evidence that IOP variation was an independent risk factor for progression (3,33). In the EMGT, patients with the highest IOPs had the highest IOP fluctuations, while patients with low IOPs had the lowest IOP fluctuations (3). On the other hand, they could confirm the strong effect of mean IOP on development or progression of glaucoma. Differences in methodological and statistical analyses have been suggested to be responsible for these discrepant findings between AGIS and EMGT (37). As suggested by Caprioli and al's recent data, IOP fluctuation could be damaging in patients with low IOP, but mean IOP could be the predominant risk factor when the IOP is high (Caprioli J, AAO Glaucoma Subspeciality Day, 2007).

IOP in relation to Blood Pressure (ocular perfusion pressure)

Unlike IOP fluctuations, abnormal ocular blood flow physiology and large variation of ocular perfusion pressure (PP) [PP= mean ophthalmic arterial pressure (= 2/3 brachial arterial pressure) - IOP] have been proven to be significant risk factors for the damage to the ONH structure in glaucoma. The peaks and troughs in circadian IOP and BP do not necessarily occur at the same time in an individual patient. In healthy subjects, the ocular blood flow is auto-regulated through the change in resistance of vessels to keep the tissue ocular blood flow and the metabolic activity stable. If the auto-regulatory procedure is defective or if the minimum perfusion pressure reaches a threshold beyond which the metabolic activity is stopped, periods of inadequate perfusion may happen resulting in ischemia. If the ischemia is prolonged, it will result in local tissue necrosis and ganglion cell apoptosis (14, Caprioli J, AAO Glaucoma Subspeciality Day, 2007).
So patients with perfusion pressure lower than 50 mmHg are at greater risk for developing or worsening POAG whereas at 30 mmHg the risk is 4 times greater (32). Nocturnal arterial hypotension has been shown to be a risk factor in glaucoma patients (11,13,16, 23,38). This can be observed in hypertensive patients on oral antihypertensive therapy, thus implying that aggressive antihypertensive treatment may make such patients more vulnerable to progression (17).
Several population-based studies have also demonstrated the association between low perfusion pressure at baseline, reduced diastolic blood perfusion pressure (i.e equal or lower than 50 mmHg) and risk for primary open-angle glaucoma (4,39,45).
Clearly many questions are still unanswered in this field. Larger, prospective, longitudinal studies are needed to confirm the predictive ability of 24-hour IOP measurements for development or worsening glaucoma.

Clinical messages

- IOP is more variable in glaucomatous than in healthy eyes.
- 24-hour IOP fluctuation and long-term IOP variation tend to be correlated with mean IOP: eyes with higher mean IOP tend to have higher variation.
  So far, studies have shown conflicting results as to whether IOP variation constitute a risk factor for glaucoma
- Reduced perfusion pressure and reduced diastolic blood pressure have been shown to be a risk factor for glaucoma.
- Until further confirmation, it is recommended to systematically perform minidiurnal IOP curves in all newly diagnosed glaucoma patients. Recommended time points are: 8:00,10:00 am, 2:00 and 6:00 pm. Medications that have the best chance to optimally control IOP fluctuations will be privileged when large IOP fluctuations have been detected.
- If feasible, a diurnal curve with 24-hour BP recordings is recommended whenever progression is suspected despite apparent “normal” IOP’s with good compliance.
- In any case, visits should be scheduled at different times of the day.

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