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MAJOR REVIEW

Understanding the Importance of IOP Variables in Glaucoma: A Systematic Review

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Abstract. Glaucoma is one of the leading causes of visual impairment and blindness. Lowering intraocular pressure (IOP) is the only proven means to slow or halt disease progression among those at higher risk of developing glaucoma and those with early to moderate or more advanced glaucoma. Recent publications have highlighted the potential for increased rates or likelihood of worsening glaucoma among those with larger IOP swings within defined time periods. The purpose of this systematic, comprehensive review and analysis of the literature was to assess the state of knowledge in the area of IOP changes over time and the potential impact of such changes on treatment. Current literature indicates that a random IOP measurement is a poor surrogate for IOP levels throughout the day and across visits. We address several key questions: 1) What is the best way to measure IOP? 2) Should multiple IOP measurements be performed in a day in the office (short-term IOP fluctuation)? 3) Is measurement at night required? 4) Should clinicians begin to assess long-term IOP fluctuation in patients under stable treatment (across days or visits)? and 5) Should therapy choices be influenced by properties of different treatment options relative to short- or long-term IOP fluctuation? (**Surv Ophthalmol** 54:643–662, 2009.

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I. Introduction

Glaucoma is one of the leading causes of visual impairment and blindness in the United States[21,32] and worldwide.[101] Lowering intraocular pressure (IOP) is the only proven means to slow or halt disease progression in studies of those at high risk of developing glaucoma (Ocular Hypertension Treatment Study [OHTS]),[48] those with early to moderate glaucoma (Collaborative Initial Glaucoma Treatment Study[67] and Early Manifest Glaucoma Trial [EMGT])[42,66] and those with more advanced glaucoma (Collaborative Initial Normal-Tension Glaucoma Study[19,20] and Advanced Glaucoma Intervention Study [AGIS]).[2] Across all randomized, controlled trials, lowering IOP by at least 18% (mean) from baseline resulted in at least a 40% reduction in rates of worsening of glaucoma over 5 years.[20,42,66,67] These studies confirm that a pathophysiological basis for glaucoma is elevated IOP. Studies of the biomechanical properties of the cornea have improved our understanding of the effect of IOP on the optic nerve and sclera, although this understanding has not led, as yet, to a systematic effect on therapy.[17,109] The potential for increased rates or likelihood of worsening glaucoma among those with larger IOP swings within defined time periods has received increasing attention.

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In this review, we present the state of knowledge in the area of changes in IOP over time and the potential impact of such changes on the treatment of glaucoma. A longer and more detailed version of this review was used to provide information to an international expert panel that assessed whether consensus exists and the degree of consensus concerning the measurement, characterization, and potential implications of IOP and its fluctuation over time for glaucoma treatment. The current review will necessarily seek to clarify the terminology, describe the many varieties of techniques used to measure IOP changes over time, and present the relationship between different forms of IOP changes over time, treatment (medication and surgery) efficacy, and patient outcomes.

II. Terminology

A wide range of terms has been used to describe IOP changes over time. These have included (often in the same paper): IOP peak, IOP trough, IOP fluctuation, diurnal fluctuation, circadian fluctuation, circadian variation, nocturnal fluctuation, nocturnal variation, IOP variation and diurnal variation, intra-visit fluctuation and variation, and inter-visit fluctuation and variation. To date, there has been no standardized terminology, method for measurement, or recommended guidelines for the usage of these terms.

In order to logically and consistently assess and report on the literature, this review will use these terms in a defined, mutually exclusive fashion based on the majority usage in the literature. For the purposes of this review, the data in the papers will be reported in this standard terminology to facilitate comparisons and understanding.

The first dimension is the time period over which IOP is measured (Table 1). For those papers and studies that report IOP changes over a 24-hour period or less, we will use the term *short-term IOP fluctuation*. For those that report on IOP that differs from visit to visit on different days, we will refer to this measure of changes of IOP over time as *long-term IOP fluctuation*.

Second, use of the term *nocturnal* will mean measurement during sleeping hours (typically an 8-hour period at night or in a darkened room). Because it is used exclusively in the literature in studies performed within a 24-hour time period, its use will denote that time period, even if used as "nocturnal variation" as well as "nocturnal fluctuation." Similarly, *circadian* will be defined to be within 24 hours, even if associated with the term *variation*. Within each time period, *IOP peak*[11] is the highest IOP recorded in that stated time period, and *IOP trough* the lowest IOP recorded in that stated time period.

TABLE 1

Standardized Terms Describing Intraocular Pressure (IOP) Changes Over Time

- *IOP*: A measure of the pressure inside the eye
- *IOP peak*: The highest IOP recorded in a stated time period
- *IOP trough*: The lowest IOP recorded in a stated time period
- *Short-term IOP fluctuation*: IOP peak minus IOP trough measured in a stated time period, understood to be 24 hours or less (intra-visit):
  - o Circadian
  - o Nocturnal
- *Long-term IOP fluctuation*: IOP peak minus IOP trough measured in a stated time period, understood to be on separate days (inter-visit)

Putting these together, the description *short-term IOP fluctuation* reflects the IOP peak minus the IOP trough in a stated time period, again generally understood to be 24 hours or less.[9,10,47,122] When evaluating IOP fluctuation over a period of time greater than 24 hours,[8,11,90] the term *long-term IOP fluctuation* represents the IOP peak minus the IOP trough from visit to visit.

III. Issues and Significance of Measuring IOP

A. METHODS OF MEASUREMENT

The current gold standard for IOP measurement in the laboratory setting is manometry; however, the use of such manometric devices is not feasible in routine clinical care. IOP measurement in the office generally is obtained using one or more of the following instruments: the Goldmann applanation tonometer (GAT), the Tono-Pen (Medtronic Solan, Jacksonville, FL), the Pascal dynamic contour tonometer (DCT; Ziemer Ophthalmic Systems AG, Port, Switzerland), and the pneumotonometer (Table 2).[14,26,29,49,53,55,62,86]

1. Goldmann Applanation Tonometer

Goldmann applanation tonometry remains the gold standard for in-office, routine IOP measurement. The portable GAT (Perkins) offers the same accuracy as slit-lamp-mounted applanation tonometry with the advantage of examining the patient regardless of position. The accuracy of both techniques depends on factors such as corneal thickness, corneal curvature, corneal structure, and axial length, all of which may affect the IOP measurement.[86] Assessments show that