Comparison between intraocular pressure profiles over 24 and 48 hours in the diagnosis of glaucoma

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Abstract

Purpose: To assess the additional value of 48-hour diurnal-nocturnal IOP profiles in comparison to only 24-hour diurnal-nocturnal IOP profiles in the management of glaucoma.

Methods: All diurnal-nocturnal IOP profiles over 48 hours that were taken between 2017 and 2019 for diagnostic purposes in glaucoma patients at our hospital were reviewed. We counted elevated IOP values (>21 mmHg), higher short-term IOP fluctuations (> 6 mmHg) and nocturnal IOP peaks (measured at midnight and at 7 AM in supine position). In a second step, we repeated this analysis in the same profiles but censored the data to the first 24-hours. We compared the outcome rates by means of the Chi^2-Test.

Results: 661 IOP profiles were included. 59% of 48-hour IOP profiles revealed IOP values above 21 mmHg and 87% showed IOP fluctuation greater than 6 mmHg. Nocturnal peaks in supine position could be observed in 51% of the patients. In the profiles censored to the first 24 hours, the fractions were 50%, 71% and 48%, ($p < 0,01$, $p < 0,01$ and $p = 0,12$) respectively.

Conclusion: Our data suggest that 48-hour diurnal-nocturnal IOP profiles are superior in identifying patients with clinically meaningful IOP events in comparison to observing the patients for only 24-hours. It is likely that the higher accuracy is worth the additional socioeconomic costs resulting from the prolonged inpatient stay.

Introduction

Glaucoma is characterized by a progressive loss of retinal ganglion cells and represents one of the leading causes of blindness worldwide [1–3]. Several risk factors for the emergence and progression of glaucoma have been described including older age, family history of glaucoma, exfoliation, lower systolic blood pressure and elevated intraocular pressure (IOP) [4, 5]. Among these, elevated IOP is most important, since lowering the IOP has been shown to be the only therapeutic approach to reduce the risk of progressive loss of ganglion cells and therefore visual field loss [6]. In healthy humans, the IOP usually ranges from 10 to 21 mmHg and shows a significant fluctuation over the period of 24 hours [7, 8]. Whether IOP fluctuation is an independent risk factor for the progression of glaucoma has been the subject of debate in recent years with some studies suggesting intraocular IOP fluctuation to be an independent risk factor for the progression of glaucoma, and some studies suggesting otherwise [9]. For example, Tajunisah et al. reported a mean IOP amplitude of 6 mmHg in glaucoma suspects compared to 4 mmHg in healthy eyes [10]. It has been shown, that IOP frequently peaks at night. This is usually attributed to a supine sleeping position and circadian rhythm [11].

With elevated IOP being the only treatable risk factor for visual field loss in glaucoma patients, it is of utmost importance to detect high IOP values and identify those patients who should be considered for IOP lowering therapeutic measures. IOP is usually measured within normal office hours in an outpatient setting. However, it has been shown that sporadic IOP measurements often fail to reproduce IOP mean values due to IOP fluctuation and the diurnal and nocturnal changes mentioned before [12]. In many

places, glaucoma patients with suspected progressive visual field loss and seemingly normal IOP values are hospitalized and the IOP is measured repeatedly in order to approach the true mean IOP and rule out considerable IOP peaks [13]. However, it has been shown that diurnal pressure patterns show poor repeatability both in healthy controls and glaucoma patients [14, 15]. Fischer et al. reported IOP profile data of a cohort of 80 patients who received a diurnal and nocturnal IOP profile, suggesting that both maximum and mean IOP differed between day 1 and day 2 of the profile [16].

In this study, we aim to determine the additional value of IOP profiles over 48 hours, compared to IOP profiles over 24 hours, regarding the ability to identify patients with elevated IOP values and significant IOP fluctuation. Additionally, we analyze whether potential nocturnal peaks are more frequently detected when measuring the IOP over 48 hours.

Methods

General

This retrospective mono-center cohort study was approved by the local ethics committee (vote no. 21-1184).

IOP profile baseline data and inclusion/ exclusion criteria

We manually reviewed our hospital database from the years 2017 to 2019 and identified all patients who had been admitted for an IOP profile due to suspected or manifest elevated IOP. We did not further distinguish between different types of glaucoma. The IOP profile usually starts on the first day of hospitalization at noon and is conducted over 24 or 48 hours. Timepoints of IOP measurements are 12:00, 16:00, 20:00, 00:00 and 07:00. This results in a total number of IOP measurements of 10 over the period of 48 hours and 5 over the period of 24 hours. The 12:00, 16:00 and 20:00 measurements are performed using Goldmann applanation tonometry (GAT) in a sitting position, the 00:00 and 07:00 measurements are performed using a handheld contact tonometer (iCare tonometer, iCare Finland Oy) in a supine position. Patients are instructed to adhere to their usual sleeping schedule. In this study, only IOP profiles over 48 hours were considered for further analysis. Missing IOP measurements was an exclusion criterion. Of all IOP profiles, 661 profiles matched these criteria and were included in the analysis.

Data analysis

For this study, we operationalized clinically meaningful IOP events according to the following criteria:

- At least one IOP measurement over 21 mmHg.
- IOP fluctuation over 6 mmHg over the course of the IOP profile.
- IOP maximum in one of the nocturnal measurements in supine position.

In a first step, we analyzed what percentage of all 48-hour IOP profiles fulfilled any of these criteria. In a second step, the analysis was repeated for the same dataset, albeit censored for the first 24 hours only.

Data were analysed with the R-platform [17].

Statistical testing

We used the Chi^2 test to compare event rates between groups. The alpha level was set to 0.05. We did not correct for multiple testing.

Results

Detection of elevated IOP

The share of IOP profiles that showed an IOP above 21 mmHg at least once within 48 hours was 59%. When only the first 24 hours of every IOP profile were considered, this percentage was only 50%. This means that 9% of eyes showed elevated IOP values only during the second day of the IOP profile. The difference was statistically significant ($p < 0.01$).

IOP fluctuation

In 87% of all eyes, the IOP showed a fluctuation of above 6 mmHg over the period of 48 hours, whereas this was the case in 71% of the profiles when only the first 24 hours were considered. This result was statistically significant ($p < 0.01$).

Time point of maximal IOP

We analyzed whether the highest IOP of every IOP profile was measured in one of the nocturnal measurements (00:00 or 07:00, supine position). This was the case in 51% of the profiles over the period of 48 hours, and in 50% of the cases when only the first 24 hours were considered. The difference was statistically not significant ($p = 0.12$).

All results are shown in Table 1.

Table 1
Fractions of IOP profiles that met the predefined criteria for the 24 hour and the 48 hour group.

	After 24 hours	After 48 hours	Chi^2 Test
$T_{max} > 21$ mmHg	50%	59%	$P < 0.01$
IOP fluctuation > 6 mmHg	71%	87%	$P < 0.01$
IOP maxium in supine position	48%	51%	$P = 0.12$

Discussion

In this study, we present data from a comparatively large number of IOP profiles that had been collected for diagnostic purposes in our hospital. While to date there is little evidence that IOP profiles are

important to limit visual field loss in glaucoma, recent literature tends to recommend IOP measurements outside normal office hours to identify patients at risk [13, 16, 18]. However, the implementation of routine IOP measurements outside normal office hours can be challenging from a practical perspective. In Germany, costs for inpatient IOP profiles are covered by public or private health insurance in cases where glaucoma progression is suspected under treatment or nocturnal IOP peaks are suspected. Those IOP measurements are usually conducted over 24 or 48 hours in the hospital. In our study, 9% of eyes showed IOP values above 21 mmHg exclusively in the second 24 hours of measuring. Had those patients only received an IOP profile over 24 hours, they would have been at a considerable risk of undertreatment and potentially glaucoma progression. In reality, even more patients might be at risk when the IOP is insufficiently monitored because in many cases, the target IOP is even less than 21 mmHg. Our study however, by design, does not allow further or more accurate conclusions. Regarding IOP fluctuation, our data suggest that IOP profiles over 48 hours will identify more patients with significant short-term IOP variation. These findings suggest that IOP measurements should preferably be conducted over 48 hours. This is also supported by data, suggesting that diurnal IOP patterns are poorly reproducible. Furthermore, IOP profiles over 48 hours have been reported to be more reliable than IOP profiles over 24 hours regarding detection of IOP peaks and elevated IOP means [15, 16].

However, the socio-economic aspects of diagnostic efforts also have to be considered. The global prevalence of glaucoma is expected to rise in the near future and by the year 2040 nearly 112 million people could be affected by the disease [3]. For Germany, a large population-based prospective cohort study suggested a glaucoma prevalence of 1.44% in 2018 [19]. Based on a population of an estimated 83 million, this results in roughly 1.2 million manifest glaucoma cases. The economic burden of glaucoma is significant. Direct medical costs include medication, consultations or hospital visits. Examples for direct non-medical costs are transportation and public financial aid programs for the blind. Moreover, indirect costs such as loss of productivity of patients and caregivers add to the total costs [20]. Direct medical costs alone were reported to exceed 1000 euros per year in western European countries at the beginning of the century [21, 22]. More recent data from the US suggested annual direct costs of approximately 2200 dollars for stage 5 glaucoma patients [23]. In Germany, the second night of an inpatient IOP profile accounts for approximately 300 euros, which have to be covered by the patient’s health insurance. Given the diagnostic advantage of 48 hour IOP profiles our data suggest, this expense might be well invested if follow-up costs resulting from disease progression can be avoided.

Limitations Of This Study

By design, our study has certain limitations. We cannot determine whether the generation of IOP profiles per se improves anti-glaucomatous therapy or helps reducing the probability of glaucoma progression. Furthermore, our data is potentially biased because IOP events were operationalized in a simple manner irrespective of form of glaucoma or anti-glaucomatous therapy. However, due to the beforementioned criteria made by health insurances, our cohort predominantly consists of patients under intense anti-glaucomatous therapy and patients who already experienced surgical intervention to lower the IOP. The difference of 16% of patients experiencing IOP fluctuation between the 24- and 48-hour analysis should

be viewed with caution because nocturnal measurements are performed with a handheld tonometer, whereas diurnal measurements are performed using Goldmann applanation tonometry. Additionally, not all GAT measurements were conducted by the same examiner.

Conclusion

On the basis of our data, we recommend a time frame of 48 hours rather than 24 hours when IOP profiles are used as a diagnostic tool, especially in cases where IOP values were normal during the first 24 hours of the profile. However, larger and randomized clinical trials would be useful to evaluate the general diagnostic value of IOP profiles.

Abbreviations

IOP: intraocular pressure; GAT: Goldmann applanation tonometry

Declarations

Ethics approval and consent to participate: The local ethics committee (Ethics committee, University of Freiburg, Engelbergerstrasse 21, 79106 Freiburg, Germany) approved of the conduction of this study (vote no. 21-1184). According to the vote by the local ethics committee consent to participate was not needed.

Consent for publication: According to the vote by the local ethics committee consent for publication was not needed.

Availability of data: Data is available on reasonable request.

Competing interests: The authors declare that they do not have competing interests.

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Authors' contributions: PK and JL designed the study and performed data acquisition. PK, DB and JL performed statistical analysis. TR and AA helped with data interpretations. PK and JL drafted the manuscript. DB, TR and AA helped with proofreading. All authors read and approved the final manuscript.

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