Reviewer's report

Title: Instability of 24-Hour Intraocular Pressure Fluctuation in Healthy Young Subjects: a prospective, cross-sectional study

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Reviewer: Ivano Riva

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This is a nice, well-written study demonstrating that in a small sample size of 10 healthy subjects repeated 24-hour IOP measurements in 5 non-consecutive days show good agreement for maximum and minimum IOP values, both in sitting and supine position, but not for IOP fluctuation (Max IOP-Min IOP). Blood pressure shows good agreement as regards maximum and minimum systolic and diastolic values, but also for systolic and diastolic fluctuation, both in sitting and supine position, during the 5 days of assessment. All measurements were done without limiting patients’ daily activities and habits, reflecting real-life conditions. There are a few errors in the English language. Small sample size and only-women sample must be kept in mind in generalizing results of the study. Some extra points need to be addressed.

Major Compulsory Revisions

Comment #1: Actually there is no consensus about the role of IOP fluctuation for developing POAG from OHT or for POAG progression. Several randomized clinical trials (OHTS, EGPS, EMGT) failed identifying IOP fluctuation as an independent risk factor for progression. However, other studies identified fluctuation as an important and independent risk factor for POAG progression (for example, Asrani and coll.; Konstas and coll, Journal Ocul Ther Pharmacol Ther 2012). Please expand this topic and insert proper literature references.

Comment #2: Goldmann tonometer was used for sitting IOP measurements, while Tonopen-AVIA was used for supine IOP measurements. While it’s true that this doesn’t affect the slope of 24-hour IOP curve in single body positions, more data about the agreement between the two tonometers should be added, in consideration of higher supine than sitting IOP values found in the study.

Comment #3: IOP and blood pressure fluctuations were analyzed in sitting and supine position over the 24-hour. However it would be useful to consider also a mixed curve, with sitting-IOP values during the day and supine-IOP values during the night. This would reflect closer the physiological IOP and blood pressure 24-hour curve, despite a possible systematic error due to the use of different tonometry techniques. Recent studies have shown the effect of different tonometry techniques on IOP postural change evaluation (discuss and add references).

Comment #4: Authors used Intra-Class Correlation Coefficient (ICC) to evaluate
reliability of IOP and blood pressure measurements. ICC is typically used when there are a number of different interviewers, raters or assessors within the survey. It is defined as the proportion of total variance within data that is explained by variance between interviewers. Calculating IOP fluctuation as maximum-minimum IOP, authors caused an increase in data variance (for independent variables the Bienaymé formula says: \( \text{Var}(X-Y) = \text{Var}(X) + \text{Var}(Y) \)). I suggest authors to rename “IOP fluctuation” as “IOP range” and calculate IOP fluctuation as standard deviation of IOP measurements, a more stable index.

Comment #5: Table 1, 2 and 3 should be revised. It would be interesting to see mean values of IOP, blood pressure and MOPP for every day of the study, so that data significance could have immediate impact on the reader.

Comment #6: Authors found higher supine than sitting IOP values in healthy young patients \((p=?)\), in spite of the use of different tonometry techniques, while ocular perfusion pressure was quite constant both sitting and supine \((p=?)\). A recent review by Quaranta and Coll, entitled “24-hour intraocular pressure and ocular perfusion pressure in glaucoma” (Survey of Ophthalmology, 2014) analyzed the topic in patients affected with glaucoma. Please add reference. Another recent paper by Quaranta and Coll. failed identifying a significant difference in IOP between day and night, in patients affected with OHT and POAG (IOP was measured during the day in sitting position with Goldmann tonometer and during the night in supine position with Perkins tonometer; article’s title: “Untreated 24-h intraocular pressures measured with Goldmann applanation tonometry vs nighttime supine pressures with Perkins applanation tonometry”, Eye 2010). Please compare with your results and add appropriate references.

Comment #7: A recent work by Aptel and Coll. analyzed reliability of 24-hour phasing in patients affected by OHT and POAG. They found poor agreement between two 24-hour IOP curves performed at least 6 months apart. Please add reference and compare with your results.

Comment #8: Graphs of IOP and blood pressure phasing in patient n. 6 should be substituted by more general graphs of the entire population of the study. Authors should graph maximum, minimum and fluctuation values for IOP and blood pressure during the days of the study for the entire population. This would give a better scenario of 24-hour parameters’ trend.

Minor Essential Revisions
Comment #9: Please correct reference n.1 (typing error)

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests