Various Ways of Continuous Intraocular Pressure Monitoring in Glaucoma Patients: A Narrative Review

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ABSTRACT

Glaucoma is a group of neurodegenerative disease linked with imbalance in the drainage of aqueous humor. Glaucoma is caused by an imbalance in the drainage of aqueous humor, which results in increased intraocular pressure (IOP) and subsequently leads to optic nerve damage and eventual blindness. Since IOP is a modifiable risk factor for glaucoma, it is essential to identify IOP variations throughout the day before initiating treatment. Monitoring IOP is a critical aspect of glaucoma management. Various techniques have been and are being used to monitor IOP continuously for 24 hours to determine peak IOP and pressure fluctuations. This review aims to discuss innovative approaches and highlight the importance and limitations of each technique in obtaining an IOP profile over 24 hours.

Kata kunci: fluktuasi, kanta sentuh, pemantauan, sensor, tekanan intraokular, tonometri sendiri, transduser

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Glaucoma is a group of neurodegenerative disease linked with imbalance in the drainage of aqueous humor. Glaucoma is caused by an imbalance in the drainage of aqueous humor, which results in increased intraocular pressure (IOP) and subsequently leads to optic nerve damage and eventual blindness. Since IOP is a modifiable risk factor for glaucoma, it is essential to identify IOP variations throughout the day before initiating treatment. Monitoring IOP is a critical aspect of glaucoma management. Various techniques have been and are being used to monitor IOP continuously for 24 hours to determine peak IOP and pressure fluctuations. This review aims to discuss innovative approaches and highlight the importance and limitations of each technique in obtaining an IOP profile over 24 hours.

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the aqueous humor flow due to resistance in the aqueous drainage system. This increases the intraocular pressure (IOP), which causes damage to the optic nerve head and leads to irreversible blindness. As IOP is the only treatable risk factor for glaucoma, its 24 hours biorhythm need to be understood before managing it. Monitoring IOP is a critically important part in the management of glaucoma. Various approach and technology have been initiated and on-going for a frequent, round-the-clock IOP measurement to determine the IOP peaks and fluctuations. We review the current innovative approach and its importance as well as discussing the shortcomings of each method to obtain the 24 hour IOP profile.

Keywords: contact lens, fluctuation, intraocular pressure, monitoring, self-tonometry, sensor, transducer

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INTRODUCTION

Glaucoma is the second leading cause of vision loss in the world and it is estimated that 10% of people affected by glaucoma progress to blindness. In a systematic and meta-analysis study in 2013, the number of people who suffered from glaucoma worldwide, was 64.3 million and 60% of this figure was from the Asian region, with 53.4% diagnosed with primary open angle glaucoma. The number of patients diagnosed with glaucoma in the world are estimated to increase to 76 million for the year 2020 and 111.8 million by 2040 (Tham et al. 2014). Glaucoma, often called as 'silent thief of vision' is characterized as a group of diseases causing progressive damage to the optic nerve head which leads into peripheral visual field loss and subsequent irreversible blindness.

Although there are various risk factors which cause the progression of glaucoma, assessment of intraocular pressure (IOP) is a critical aspect in the management for patients with glaucoma. Studies suggested elevated IOP was one of the significantly important (Weinreb & Khaw 2004) and modifiable risk factor in the progression of glaucoma as reduced IOP delays and prevents the onset of the disease (Kass et al. 2002; Heijl et al. 2002). Progression of the disease was less frequent and occurred significantly later when IOP reduction was maintained by 25% lower with medication (Heijl et al. 2002). With each millimetre of mercury of IOP reduction, the progression risk was decreased by about 10% (Leske et al. 2003). During clinical practice, clinicians do encounter progressive visual field loss in glaucoma patients despite single value of IOP measurement in the acceptable range. Hence, studies to relate the association between progression of visual field loss and the occurrence of IOP peaks were done. It was found patients with progressive visual field loss have significantly more frequent IOP peaks than patients with stable visual field (Zeimer et al. 1991) supporting peak IOP as an independent risk factor for
glaucomatous progression (Konstas et al. 2012). Several studies have hypothesized that IOP fluctuation is another risk factor for disease progression. The range, the diurnal/nocturnal range and the day to day variation are three parameters in IOP fluctuation. Large fluctuation of IOP in a day or in several consecutive days is a strong and enhanced risk factor for the glaucoma progression (Asrani et al. 2000). Some investigators from Advanced Glaucoma Intervention Study (AGIS) team have reported visual field progression of approximately 30% in every 1 mmHg IOP fluctuation for every 5 years increment of age (Nouri-Mahdavi et al 2004). A diurnal fluctuation of more than 6 mmHg was recorded occurring significantly more frequent in the glaucomatous group than in the normal eyes (Sihota et al. 2005). Glaucomatous damage was found to be severe when IOP fluctuations were greater in the eyes with low mean IOPs whilst the role of IOP fluctuation become less important when the mean IOP is higher (Caprioli & Coleman 2008).

However, there has been some controversy in IOP features as some studies have shown different results. Bengtsson & Heijl (2005) reported IOP fluctuation was not an independent risk factor for glaucoma development in a group of patients with high-risk ocular hypertension. They followed patients for every 3 months for 10 years and the IOP variation was computed in 3 different variability: mean range of each diurnal tension curve (daily range), mean value of maximum IOP in all tension curves and the range between the lowest and highest IOP of all measurements. A study by Early Manifest Glaucoma Trial (EMGT) has yielded that mean IOP is a strong factor for glaucoma progression and IOP fluctuation has no relationship with the disease progression (Bengtsson et al. 2007). Another study by Medeiros and his team also evaluated long-term IOP fluctuation towards glaucoma progression and their result agreed with EMGT study, that, IOP fluctuation was not associated with glaucoma progression in untreated ocular hypertensive subjects (Medeiros et al. 2008). Both EMGT and Medeiros and team study defined the IOP fluctuation as standard deviation of IOP measurement obtained during different visits throughout the study period.

Hence, for better understanding on IOP behaviour in glaucomatous patients and its influence on disease pathogenesis and management, a number of investigators have prompted to closely and continuously monitor the IOP for a 24-hour period. IOP is a dynamic parameter with circadian rhythm and various ways and approaches to measure the IOP round-the-clock were developed in the field.

A 24-hour IOP Monitoring and its Importance

Often in clinical practise, the Ophthalmologist relies on sporadic IOP measurement which is obtained during office hours. This single IOP measurement is not sufficient for optimal glaucoma management as it may not provide adequate information
on IOP behaviour during the entire 24 hours period. Despite well controlled IOP obtained with adequate glaucoma treatment, some patients still continue to develop the disease progression (Zeimer et al. 1991; Chauhan & Drance 1992). This could be possibly due to occurrence of IOP peaks and IOP fluctuations outside of normal office hours, which is not detected during routine examination (Asrani et al. 2000; Barkana et al. 2006). Diurnal IOP curve definitely provides a better estimation than an isolated office reading on a subject’s IOP variation (David et al. 1992). However, this do not cover the measurements of IOP early evening to nocturnal sleep period. In another study, elevation of IOP at night was observed toward the end of the 8 hours assigned sleep period which is not due to pupillary dilatation in darkness as elevation was detectable even under moderate illumination (Liu et al. 1999). Large variation in diurnal IOP was found in the glaucoma group either in sitting or supine position. Nocturnal supine IOP was greater during sleep than the diurnal sitting IOP and a nocturnal increase in supine IOP was observed from the level measured before the sleep (Liu et al. 2003). Another study suggested that IOP increases profoundly when subjects were asleep in the dark and IOP was highest on awakening in the early morning. Their study noted that IOP decreased very rapidly once the subject was awake and sitting in a vertical position (Frampton et al. 1987).

Hence, various studies have shown the effect of IOP is continuous and within an individual patient, measurements of IOP have significant variability throughout 24 hours. There can be spontaneous rise in IOP when going from upright to inverted body positions and overall the magnitude of the IOP change is greater in glaucomatous eyes. The fact is that highest IOP occurs outside office hours in glaucoma patients and these IOP peaks can be undetected unless a continuous 24 hours IOP monitoring method or device is used to provide a complete IOP profile. The approach in using these devices towards continuous monitoring of IOP has three different strategies: self-monitoring of IOP by the patient, permanent IOP monitoring and temporary IOP monitoring. The search for device to give round the clock IOP measurement started 50 years ago, but only recent technology advances have provided clinical investigators with some devices which could provide more information and identify dynamic patterns of IOP. Table 1 shows various methods and devices for continuous IOP monitoring.

**Phasing with Applanation Tonometry**

Applanation tonometry measures IOP by providing force which flattens the cornea and the opposing force of the corneal rigidity and tear film are allowing the pressure in the eye to be determined. It is based on the Imbert-Fick law, which assumes that the eyeball is spherical in shape and the cornea is an infinitely thin, elastic and flexible structure. Variable force applanation tonometers (e.g: Goldmann, Perkins, Pneumatonometer) are used in
the research field and Goldmann applanation tonometry (GAT) remains the gold standard for fast and reproducible IOP measurements. The output measurement of these devices is in mmHg. Investigators in the field have used these instruments for continuous monitoring of IOP and managed to produce diurnal tension curve (Bengtsson & Heijl 2005) and 24 hours circadian profiles (Barkana et al. 2006). Diurnal tension curves are multiple recordings of IOP measured at different time points during office hours but it does not represent the values of IOP during night. Whilst, a 24 hour circadian profile gives an insight on IOP measurements recorded on both day and night time (nocturnal period). Night time IOP measurement can be collected by patients’ hospitalised or in a sleep laboratory. However, these can be inconvenient for the patient, costly and requires frequent awakening of patients for measurements which can cause physiological reactions and

<table>
<thead>
<tr>
<th>Technique</th>
<th>Device (Name and model)</th>
<th>Manufacturer</th>
<th>Comments</th>
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| Applanation            | Goldmann Tonometer      | Haag Streit, UK                   | - Routine office setting  
- Gold standard |
|                        | Perkins Tonometer       | Haag Streit, UK  
- Clement Clarke, Canada | - Routine office setting  
- Evaluation under anesthesia  
- Portable |
|                        | Pneumatonometer         | Reichert Technologies, US         | - Evaluation under anesthesia  
- Routine office setting in patient with corneal disease |
| Self Tonometry-        | Ocuton S                | EPSa Elektronik & Praezisionsbau, Saalfeld, Germany | - Portable, hand-held  
- Self measurement by patient  
- Anesthesia required |
| Applanation            | iCare Tonometer         | Tiolat Oy, Helsinki Finland      | - Portable, hand-held  
- No anesthesia required  
- Self /home monitoring  
- Screening purpose  
- Easy to use  
- Suitable for paediatric patients |
| Self Tonometry-        | iCare ONE               | iCare Finland Oy                  | - Permanent IOP monitoring  
- Surgery required (cataract surgery)  
- No corneal properties interference |
| Rebound                | iCare PRO               | iCare Finland Oy                  | - Non-invasive  
- Outpatient compatible/  
Patient’s ambulatory setting  
- Continuous IOP monitoring up to 24 hours  
- Output signal is in electric voltage, mV |
|                        | iCare HOME              | iCare Finland Oy                  | - Non-invasive  
- Outpatient compatible/  
Patient’s ambulatory setting  
- Continuous IOP monitoring up to 24 hours  
- Output signal is in electric voltage, mV |
|                        | iCare ic100             | iCare Finland Oy (Espoo,Finland)  | - Non-invasive  
- Outpatient compatible/  
Patient’s ambulatory setting  
- Continuous IOP monitoring up to 24 hours  
- Output signal is in electric voltage, mV |
| Intraocular telemetry  | Wireless Implantable    | Implantdata GmbH, Hannover, Germany | - Permanent IOP monitoring  
- Surgery required (cataract surgery)  
- No corneal properties interference |
|                        | Transducer (WIT)        | - Non-invasive  
- Outpatient compatible/  
Patient’s ambulatory setting  
- Continuous IOP monitoring up to 24 hours  
- Output signal is in electric voltage, mV |
| Contact lens sensor    | Sensimed Triggerfish    | Sensimed S.A., Switzerland        | - Non-invasive  
- Outpatient compatible/  
Patient’s ambulatory setting  
- Continuous IOP monitoring up to 24 hours  
- Output signal is in electric voltage, mV |

Table 1: An overview of various devices and methods for continuous IOP monitoring.
affect the steady state IOP at night (Liu et al. 1999; Liu & Weinreb 2011). Moreover, using the applanation tonometer requires instillation of topical anaesthetic and presence of experienced personnel to take the measurement. This method can be challenging or impossible for paediatric patients and for those having corneal abnormalities. As noted in previous studies, change in body position, from supine to sitting position has a significant impact on IOP value and there may be artefacts related to sleep interruption produced as the subjects awake from sleep state for nocturnal IOP measurement, regardless of what techniques or tonometers are used. Furthermore, measurement by GAT can be influenced by operator bias.

Self-Tonometry

Various self tonometry devices have been used for measuring and monitoring the IOP over the years (Kothy et al. 2003; Munkwitz et al. 2008; Liang et al. 2009). The latest self- tonometry instruments are based either on principles of rebound tonometry or applanation tonometry. The rebound technology uses a light weight probe which makes a momentary touch on the cornea. An induction based coil system is used for measuring the motion parameters of the probe. An advanced algorithm combined with a software analyses the deceleration and the contact time of the probe with the cornea. Deceleration and contact time of the probe changes as a function of IOP. The higher the IOP, the faster the probe decelerates and the shorter the contact time. Various model of rebound tonometry are used. The common ones are iCare rebound tonometer (Tiolat Oy, Helsinki Finland) and Icare ONE (Icare Finland Oy, Espoo, Finland). Rebound tonometry does not requires anaesthetic and it is safe, easy to handle and well tolerated by patients as there is excellent patients comfort during measurement (Munkwitz et al. 2008; Rosentreter et al. 2011). The instrument is lightweight, portable and a slit lamp is not required enabling measurement for disable patients or for screening purpose in rural areas. The measurement is rapid which makes it convenient for non-compliant patients. IOP measurement using this technique has shown good agreement with Goldmann applanation tonometry (GAT) values (Rosentreter et al. 2011; Tarkkanen et al. 2010; Brusini et al. 2006) but it tends to overestimate the IOP value if corneal thickness increases (Rosentreter et al. 2011; Brusini et al. 2006). Some other studies have noted that this technique gives poor correlation in the high IOP range but acceptable agreement with the GAT in the moderate to low range IOP level (Munkwitz et al. 2008).

Self-tonometry device that uses principle of applanation tonometry requires instillation of anaesthetic drop. Hence, there is a tendency for abuse of local anaesthetic application during the measurement as well as there is a possibility of non-compliance by patients coming for follow up on optic disc examination and visual field evaluation if knowing their IOP is within normal range. The Ocuton A and Ocuton S tonometers (EPSa Elektronik
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are hand held, portable applanation tonometers which calculate IOP electronically. The Ocuton S can be used by the patient without medical expert assistance in a sitting or supine position and minimal training is required for the patient to do self-measurement accurately and reliably (Kothy et al. 2003; Kothy et al. 2001). However, this method can be tough for patients with hand tremor and family member’s assistance may be required. Wrong positioning (decentering) of the tonometer and rapid lid closure may cause unsuccessful measurements (Theofylaktopoulos et al. 1999). Although it uses the same principles as GAT, the IOP values measured by these tonometers are overestimated by 2 to 5 mmHg compared to GAT (Kothy et al. 2003; Theofylaktopoulos et al. 1999) in spite of being able to detect IOP spikes or elevations in the diurnal curve (Kothy et al. 2003; Kothy et al. 2001). The measuring technique could contribute for this difference. Another study revealed these instrument overestimates the values during day time compared to GAT, however, during sleep/nocturnal period, GAT value was higher than the self-tonometry reading (Kothy et al. 2001). This elevation in IOP values in GAT recording is possibly due to increase in corneal thickness. Overall, self-tonometry is a good approach of IOP monitoring for glaucoma patients as it does not require any medical assistance or hospitalization and makes it possible to measure IOP day and night without interruption to their daily activities at home. Self-tonometry has helped in identifying large variations of IOP which contributes to providing immediate medical care and preservation of vision for glaucoma patients. Nonetheless, this method still requires patients awakening for nocturnal measurements which could disturb steady state sleep of the patients and induce stress related artefacts.

Eye Implant

Surgerical implant is a permanent IOP monitoring technique in which data are collected for a very long period of months or years. The wireless implantable transducer (WIT) (Implandata GmbH, Hannover, Germany) is a telemetric IOL sensor, implanted in the ciliary sulcus during a cataract surgery. WIT is a miniature in-vivo device that incorporates pressure sensors, temperature sensors, identification encoder, analogue to digital encoder and atelemetry with a micro electromechanical system application-specific integrated circuit. This entire system is supported by an external reading device which is held approximately 5cm from the transducer. The signals (data) from the transducer is being transmitted to the reader which converts from analogue to digital information and displays the IOP value on its LED display. This reading device can store up to 3000 IOP values and the memory can be enhanced if needed. WIT estimates the true value of IOP without the interference of corneal properties and this IOP measuring technique is possible to be used among patients with keratoprosthesis. This sensor
is biocompatible with human eyes and no intraocular inflammation or fibrosis was noted over one year of insertion (Melki et al. 2014). However, another study has reported anterior chamber inflammation which is due to the size and mechanical stress induced by the sensor on the anterior eye segment despite of the sensor being well tolerated (Koutsonas et al. 2015). Patients can perform IOP measurements by themselves actively at ease using the reading device without disrupting their daily activities. (Melki et al. 2014; Koutsonas et al. 2015; Koutsonas et al. 2016). Despite one study showing a satisfactory agreement between WIT and GAT (Melki et al. 2014), this technique needs to be evaluated more in further studies as the current data using human eyes are relatively small. A study on non-human data shows IOP measurements with WIT gives good repeatability results and is convenient as there is no interactions of clinicians needed (Paschalis et al. 2014). Another animal study also has shown excellent biocompatibility and reproducibility results as well as good agreement in IOP measurement between WIT and manometers. However, a downward shift in IOP measurement is noted which necessitate further investigation for device calibration (Todani et al. 2011). The limitation of this technique would be safety risk related to surgery procedures and this approach is restricted to only a group of patients who requires cataract surgery. As not many studies have been done on the human eye, certain risks need to be ruled out, such as the potential of device failure after implantation and potential leakage of toxic material if the hermeticity of the transducer is interrupted.

Contact Lens Sensor

Recently, a soft contact lens sensor has been developed to temporarily monitor IOP continuously up to 24 hours in a home setting and allows normal activity including sleep. Sensimed Triggerfish (by Sensimed AG, Lausanne, Switzerland) approved by FDA and CE marked, is a non-invasive, safe and sensitive sensor which could record the 24-hour biorhythm of biological parameter of the IOP. The Triggerfish system comes with a contact lens sensor, an antenna, a flexible cable, portable recorder and software system. With its revolutionary technology, Sensimed Triggerfish sensor is a disposable soft silicone contact lens embedded with a strain gauge (micro electromechanical system sensor) which discovers the spontaneous circumferential changes at the corneo-scleral junction that indicates the fluctuations of IOP, providing valuable information that can be useful for glaucoma treatment. The principle of the lens is to measure the corneal deformation due to the IOP as it is believed there is a correlation between IOP and corneal curvature (Leonardi et al. 2004). The silicone material of the CL is highly permeable to oxygen (125 x 10-9Dk/t units) making it possible for 24 hours continuous wear. The antenna (peri-orbital adhesive patch) is placed around the measuring eye which receives the signals wirelessly
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from the contact lens sensor. A thin flexible cable is connected from the antenna to the recorder to transmit the information from the contact lens. The portable recorder collects and stores all the data from the sensor during the monitoring session. And finally, once the 24 hours recording is done, the data is transferred via bluetooth from the recorder to the software installed in the clinician’s computer. The software processes the data into a qualitative 24 hours IOP profile of relative pressure peaks and pattern (Figure 1). The sensor comes in three different curvature sizes to give an optimum fitting for every patient with different corneal sizes. This sensor measures for 30 seconds in every 5 minutes interval during the 24 hours storing up to 288 data points. The sensor measurements are in electric arbitrary units (millivolts) referenced against a starting value of 0 eqmV at each recording point. A booklet is given to the patient to record all his/her activities which include meal times, drops instillation, physical activities and sleep period. This may help to understand and rule out any effect of the activity towards the IOP biorhythm change. Patients may continue using all anti-glaucoma drops and also artificial tears in case of any discomfort or dryness felt during the 24 hours monitoring session.

Studies have been on-going in this field to demonstrate the ability of the entire system. This sensor gives good comfort, well tolerated and is safe to use (Mansouri et al 2013; Mansouri et al. 2012; Lorenz et al. 2013) as well as, has promising results on functionality for 24 hours IOP monitoring (De Smedt et al. 2012). The sensor is fairly sensitive in detecting and distinguishing the 24-hour IOP rhythm and it gives accurate and repeatable results throughout the entire monitoring session (Mansouri et al. 2013; Mansouri et al. 2012; Mottet et al. 2013). However, this technique is prone to cause some adverse effects that are known to occur with any extended wear soft contact lens prescribed for vision corrections. The most common adverse effects are like blurred vision, conjunctival

![Figure 1: A 24-hour IOP profile measured by the contact lens sensor. Activities of the patient are noted at the bottom of the graph and the grey shades in the profile shows sleeping period of the patient. (Source: Sample monitoring done in our clinic for investigation purpose)](image-url)
hyperaemia and superficial punctate keratitis (Mansouri et al. 2012). Although these adverse effects are statistically significant, but clinically it is not notable as all events can be resolved within two days. As in other extended soft contact lens overnight wear, change in central corneal thickness is also noted after 24-hour Triggerfish contact lens wear which causes corneal curvature irregularities and leads to increase in astigmatism power (Hobanova et al. 2014). This raises a query as to whether this steepening of corneal scleral angulation could affect the signal recorded by the lens. To clear this doubt, a study to assess the effect of overnight wear of a Triggerfish sensor was conducted and the outcome of this study ruled out the influence on the IOP measurement by the sensor due to increase in central corneal thickness during the 24-hour contact lens wear (Freiberg et al. 2012).

With this smart contact lens sensor method, only one eye can be measured at a time and metal frames are not allowed to use during the monitoring session as it interrupts the measurement and causing a pause in the IOP profile. During sleep period, eye lid impact could affect the sensor measurement and there is a risk of sensor failure for unknown reason during the monitoring session which requires repetition of monitoring, thus, stressing the patient. Nevertheless, this device has crucial advantage as it can record IOP fluctuation in ambulatory setting for up to 24 hours, including during undisturbed sleep. The major challenge faced by the clinician using this system is in the analysing and interpreting the IOP profile obtained by the contact lens sensor, since the output signal is not in definitive IOP measurements (mmHg) but in electric voltage, mV. The connection between the device output and IOP is difficult to interpret and verify. If this can be resolved in the near future by translating the arbitrary values into clinical units through an algorithm, the IOP profile can be interpreted at ease.

The Necessity of 24-hour IOP Monitoring in Clinical Practice

IOP is not a single static number; it fluctuates throughout 24 hours. A uniform reduction of IOP throughout 24 hours is a therapeutic target for all clinicians to prevent glaucomatous damage. Thus, the availability of a 24 hour IOP monitoring system in clinical practice using the various devices and methods is a sign of paradigm shift in the field of glaucoma as this will improve the diagnosis and management of glaucoma in multiple ways:

i) Early detection and prevention of the disease
The availability of 24 hour IOP profile can reveal unfavourable IOP patterns which may indicate the risk factor for glaucoma onset and progression. Hence, improved treatment plan based on the timing or frequency of IOP fluctuation can be formulated.

ii) Individualised therapy
Clinicians can observe the effect of anti-glaucoma eye drop dosing or medical intervention on IOP rhythm
throughout the 24 hour period. This can facilitate appropriate or modified treatment plans.

iii) Improved adherence
Lack of understanding and insufficient knowledge of the disease among the glaucoma patients can reduce the adherence to medical treatment. Thus, showing and explaining the uncontrollable IOP patterns profile to the patients and discussing the impact of medical therapy on IOP may improve adherence to treatment.

CONCLUSION
A round-the-clock IOP monitoring can give an enormous insight about the IOP profile, effectiveness of IOP-lowering intervention on IOP patterns as well as characteristics of nocturnal IOP on glaucoma progression. Certain aspects of the IOP profile such as fluctuations, IOP peaks, the size and duration of the IOP rise during night sleep period gives important and useful information to individualise the treatment or therapies for glaucoma patients. Hence, the development of 24 hours ambulatory IOP monitoring tools is vital in the field of glaucoma management.

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Received: 7 Jun 2019
Accepted: 25 Sept 2019