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REVIEW

The Benefit of Nocturnal IOP Reduction in Glaucoma, Including Normal Tension Glaucoma

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Abstract: Nocturnal intraocular pressure (IOP) profiling has shown that the peak IOP usually occurs at night, particularly in patients with glaucoma. Multiple studies have demonstrated that these nocturnal IOP elevations drive glaucomatous progression, often despite stable daytime IOP. Existing vascular dysregulation and decreased nighttime blood pressure compound the damage via low ocular perfusion pressure while elevated nocturnal IOP disrupts axonal transport. These findings are consistent with studies that indicate lowering nocturnal IOP is important for slowing glaucoma progression. Many of the current treatment options lower nighttime IOP significantly less than daytime IOP. Non-invasive IOP-lowering treatments that effectively lower nocturnal IOP remain an unmet need in the treatment of glaucoma.

Keywords: glaucoma, nocturnal intraocular pressure, translaminar pressure differential

Introduction

Nocturnal intraocular pressure (IOP) elevation has been implicated in the progression of open-angle glaucoma (OAG) and its subtypes, including normal-tension glaucoma (NTG).[1–3] Published work has highlighted the importance of decreasing nocturnal IOP to limit glaucomatous progression, particularly in more vulnerable patients such as those with NTG.[4] NTG is a subtype of OAG that is difficult to treat with standard options like drops, laser trabeculoplasty, and minimally invasive glaucoma surgery (MIGS) because of a lower baseline IOP.[4–8] The importance of lowering nocturnal IOP and its impact on disease progression has been reinforced by studies evaluating 24-hour IOP data.[4]

Multiple studies have explored 24-hour IOP profiles and highlighted the dynamic nature of IOP.[9–12] The measurement of IOP over a 24-hour time frame has shown that peak (acrophase) IOP primarily occurs at night, particularly in patients with glaucoma.[2,3,13,14] Figure 1 demonstrates a typical pattern of nocturnal IOP elevation. Nocturnal IOP elevation is influenced by a multitude of factors including circadian rhythm and body position.[15,16] The circadian rhythm of IOP is regulated by the suprachiasmatic nucleus (SCN) with both glucocorticoids and the sympathetic nervous system potentially playing significant roles.[17] A number of approaches have been utilized to explore 24-hour IOP profiles including the use of overnight measurements in sleep labs,[18] a contact-lens sensor[11,19] (SENSIMED Triggerfish®, SENSIMED AG, Lausanne, Switzerland), and now implantable IOP sensors[9] (EyeMate®, Implandata Ophthalmic Products, Hannover, Germany). Further, multiple 24-hour IOP sensors are under development with some achieving FDA breakthrough designation, highlighting the importance of recognizing and treating elevated IOP, 24-hours a day.[20] Data from studies evaluating 24-hour IOP profiles have consistently demonstrated that nocturnal IOP elevation is more common in glaucoma patients and leads to glaucomatous progression in OAG patients, including those with NTG.[12,14]

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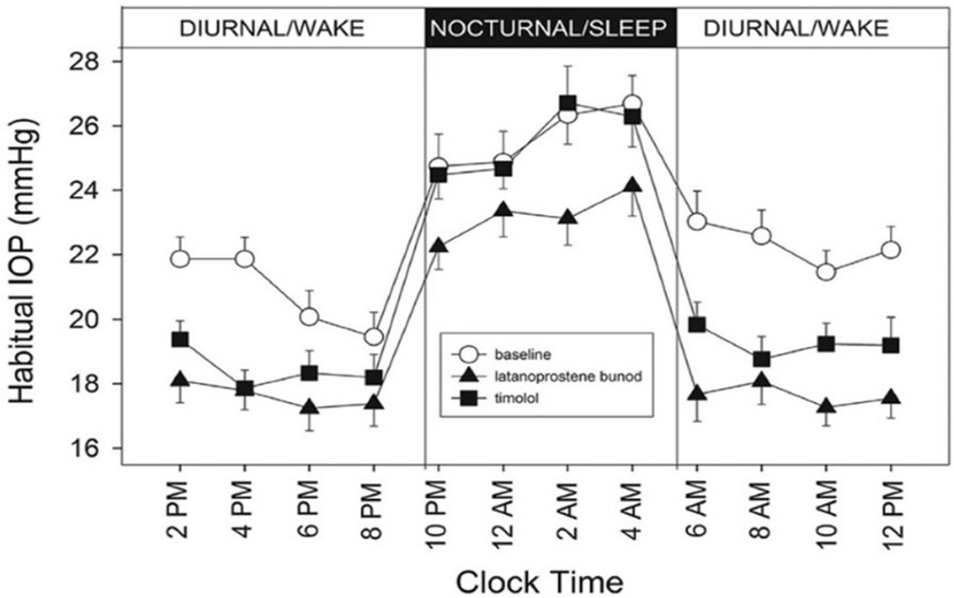

Figure 1 Nocturnal IOP acrophase, as measured in patients with ocular hypertension or early POAG (n=21).
Note: Liu JHK, Slight JR, Vittitow JL, Scassellati Sforzolini B, Weinreb RN. Efficacy of Latanoprostene Bunod 0.024% Compared With Timolol 0.5% in Lowering Intraocular Pressure Over 24 hours. *Am J Ophthalmol*. 2016;169:249–257. Creative Commons.[13]

The Early Manifest Glaucoma Trial demonstrated that every 1 mmHg decrease in IOP is associated with a 10% decrease in glaucomatous progression.[21] Studies have also shown that decreasing the total IOP burden, the area under the curve, slows glaucomatous progression.[22] Thus, strategies targeting IOP reduction remain the foundation of glaucoma treatment. Although there have been considerable advances in treatment options over the past decade, there remains a need for improved 24-hour IOP control and monitoring. A recent joint paper[23] by the American Glaucoma Society (AGS) and American Society of Cataract and Refractive Surgeons (ASCRS) emphasized this notion by stating that: (a) 24-hour IOP monitoring/control, and (b) non-invasive therapeutics that lower IOP and improve ocular blood flow were unmet needs, "especially in challenging patients who do not adequately respond to current therapies or those in whom IOP is already within the normal range".

In this report, we review:

- The impact of nocturnal IOP elevation on glaucomatous progression
- The importance of decreasing nocturnal IOP on slowing glaucomatous progression
- The rationale for why lowering nocturnal IOP elevation is beneficial
- Potential future therapies for improved management of nocturnal IOP elevation

Impact of Nocturnal IOP Elevation on Glaucomatous Progression

In the treatment of glaucoma, IOP reduction remains the only clinically-validated modifiable risk factor.[21] Clinicians nearly always rely on daytime (in-office) IOP measurements to guide treatment decisions. These measurements, however, only provide a partial snapshot of a patient's 24-hour IOP profile. It is well documented that daytime measurements often miss IOP peaks, leading to disease progression for patients whose IOP is seemingly controlled based on clinic visit measurements.[24]

A review[10] summarizes the various ways in which nocturnal IOP has been evaluated and their potential biases. There is significant heterogeneity in methodological approach, body position, and the tools used. Some performed measurements over a full 24-hours while others separated diurnal and nocturnal periods over different days since IOP can vary day-to-day and hour-to-hour. Newer tools that measure IOP as the subjects went about their regular lives have also been created. A contact lens IOP sensor (SENSIMED Triggerfish®, SENSIMED AG, Lausanne, Switzerland) showed that 70% of healthy subjects and 90% of glaucoma patients had elevated nocturnal IOP.[15] Implantable devices (EyeMate®, Implandata Ophthalmic Products, Hannover, Germany) attempt to more accurately capture true IOP through continuous monitoring that bypass biases attributed to measurements using the cornea. Several studies have confirmed their safety and accuracy[25–28] compared to Goldmann applanation and can confirm nocturnal IOP elevations without disturbing sleep. Insurance coverage for these devices and therapies that can lower nocturnal IOP would allow more equitable access to quality data and improved treatment for the benefit of patients.

The introduction of continuous 24-hour IOP monitoring techniques has supported IOP's expected nyctohemeral rhythm and pattern of nocturnal peaks. Compared to that of healthy subjects, the nocturnal IOP elevation in glaucoma patients is not only higher, but also longer.[15,29] 24-hour IOP profiles in patients with glaucoma are more volatile, with larger amplitudes of nocturnal elevation.[15,30] A multitude of recent studies evaluating 24-hour IOP profiles have demonstrated a relationship between nocturnal IOP elevation, especially nighttime spikes, and glaucomatous disease progression.[1–4] De Moraes confirmed the pattern of peak IOP occurring at night and found that the mean peak ratio and magnitude of elevation predicted faster progression and visual field change.[11] The mean peak ratio findings in this study imply that those patients with a higher nocturnal elevation are at greater risk. An additional recent study by Yang9 found that increased elevation in nocturnal IOP correlated with faster rates of visual field loss. Furthermore, a recent study[31] in treated glaucoma, including NTG patients, found that 79% of patients with progressive glaucoma, despite an apparent controlled daytime IOP, had elevated nocturnal IOP, despite an apparent controlled daytime IOP, suggesting a strong association between nocturnal IOP spikes and disease progression. In this study, mean daytime IOP was similar between progressors and non-progressors, respectively (13.57 mmHg ± 2.16 and 13.04 mmHg ± 2.06). However, 65% of patients with progression had nocturnal IOP elevations while only 24% of those without progression did. Collectively, these studies highlight the importance of nocturnal IOP elevation and its likely impact on glaucoma progression despite a seemingly "controlled" daytime IOP.[31]

Another implication of nocturnal IOP elevation is ocular perfusion pressure (OPP), defined as the difference between mean arterial pressure (MAP) and IOP at any given time. OPP is reduced when blood pressure is low or IOP is high. Multiple large-scale studies have shown a link between low OPP and glaucomatous disease progression, including the Baltimore Eye Survey, which demonstrated a 6-fold increase in glaucoma risk in patients with reduced diastolic perfusion pressure.[32–34] A study of 24-hour IOP and blood pressure patterns in patients with NTG reported that patients with a ≥20% reduction in nocturnal BP had a higher rate (>3-fold increase) of visual field progression.[31] An additional study[35] in newly-diagnosed NTG patients revealed that lower nocturnal diastolic BP was significantly predictive of visual field progression. Overall, these studies highlight the importance of OPP in the development and progression of glaucoma while supporting the need for treatment options that lower IOP at night, a time when patients are likely most vulnerable to glaucomatous damage.

The decrease in nocturnal OPP is compounded by the vascular dysregulation present in glaucoma.[36,37] Typically, physiologic ocular blood flow is autoregulated to meet and maintain metabolic needs. Normal autoregulation involves appropriate changes to local vascular resistance in response to OPP fluctuations, such as vascular dilation to offset low OPP. Vascular dysregulation in glaucoma, however, may mean that vessels stay constricted despite low OPP, further causing insufficient blood flow of the optic nerve head (ONH) tissue.[38] Prior studies using laser doppler flowmetry have demonstrated that reducing IOP can stimulate autoregulatory responses.[39] Studies have also demonstrated that reducing IOP leads to an increase in blood flow at the ONH.[37,40] Since autoregulation and OPP is impaired in patients with glaucoma, lowering nocturnal IOP improves OPP and subsequently increases blood flow, which has been demonstrated to be protective of retinal ganglion cells in model systems.[41]

The Importance of Decreasing Nocturnal IOP to Slow Glaucomatous Progression

It is well established that IOP peaks at night, likely due to circadian rhythm and increased episcleral venous pressure inherent to the recumbent position. However, it remains unclear why there are larger degrees of elevation in patients with glaucoma.[3] It is possible that impaired trabecular outflow compounds the increased episcleral venous pressure observed at night.[16] Prior work has also shown that changes in IOP associated with positioning of the body (for example, horizontal position) are more significant in patients with glaucoma.[42] It is therefore unsurprising that studies have linked extended sleep duration to glaucoma progression. A study in >6000 patients demonstrated that longer sleep duration is associated with a 3-fold greater risk of progression in patients who slept ≥10 hours per night.[43] Regardless of the mechanism, these findings highlight the importance of decreasing the duration or magnitude nocturnal IOP could slow glaucomatous progression.

A number of studies have investigated the nocturnal IOP-lowering efficacy of treatments for glaucoma.[44] Despite the growing body of evidence supporting the role and importance of nocturnal IOP in glaucoma management, therapies that specifically target nocturnal IOP reduction are limited. At night, topical agents have reduced IOP lowering efficacy; the untreated high nocturnal IOP can dramatically decrease nocturnal OPP especially in the setting of low nighttime blood pressures.[4] Since IOP is increased by episcleral venous pressure (EVP), which is elevated at night in the horizontal position, it is no surprise that treatments like MIGS, laser trabeculoplasty, and topical medications are less effective at lowering nocturnal IOP because they do not impact EVP, except for rho-kinase inhibitors. Thus, there remains a need for better treatment options that safely and effectively lower nocturnal IOP.

Commonly prescribed topical IOP-lowering agents such as beta-blockers (timolol), alpha-agonists (brimonidine) and carbonic anhydrase inhibitors (dorzolamide) have proven daytime efficacy but have minimal effect on nocturnal IOP.[2,45,46] The only medication class to consistently demonstrate a benefit of nocturnal IOP reduction are prostaglandin analogues; however, the magnitude of IOP reduction at night is reduced in comparison with daytime efficacy.[47] A prior study by Liu investigated the nocturnal effects of timolol or latanoprost as compared with no treatment in glaucoma patients. While both agents were effective at lowering daytime IOP, timolol's nighttime efficacy was no different than the absence of treatment. Both the timolol and latanoprost groups still exhibited nocturnal IOP peaks, showing reduced efficacy at night.[46] An additional study by Liu[18] demonstrated a benefit of adding brinzolamide to latanoprost for reducing nocturnal IOP, but the difference was minimal, with all groups still demonstrating a nocturnal IOP peak.

Although prostaglandin analogues are known to lower both daytime and to a lesser degree nocturnal IOP[2,48] the necessity of a daily drop implies that the effect is cyclical. It is therefore plausible that sustained drug delivery systems like the bimatoprost intracameral implant (Durysta®, AbbVie, Chicago, IL, USA) and the travoprost intracameral implant (iDose® TR, Glaukos, Aliso Viejo, CA, USA) might provide an incremental benefit over the drop form. A recent study[49] on Durysta shows that unlike the bimatoprost drop, which lowers daytime IOP twice as much as nocturnal IOP, the Durysta implant was able to lower both diurnal and nocturnal IOP by similar amounts. Although the nighttime IOP was still overall higher than daytime, this study suggests that implantable drug delivery systems may provide better 24-hour coverage. There is yet no nocturnal data on the iDose due to the recent arrival on the market.

The recently published LiGHT trial demonstrated that although post selective laser trabeculoplasty IOP had a lower 24-hour average, its 24-hour rhythm and nocturnal peaks were similar to that of pre-treatment measurements.[50,51] Because no studies to date have investigated the 24-hour IOP profile after MIGs surgeries, it is unknown if MIGs can actually lower nocturnal IOP.[52] Most of these MIGs target the conventional pathway, which is undermined by increased nocturnal EVP. It is possible that supraciliary shunts, which bypass EVP via the unconventional pathway, may effectively lower nocturnal IOP; however there have been no 24-hour IOP studies on supraciliary shunts.

The only incisional surgical treatment shown to provide 24-hour control is trabeculectomy, which has also demonstrated the best efficacy of slowing glaucoma progression in progressive glaucoma with elevated or normal IOP. Multiple studies have been published supporting the benefit of trabeculectomy in reducing nocturnal IOP elevation, including work highlighting the superior 24-hour IOP control offered by trabeculectomy versus maximal medical management.[52–55] The minimization of nocturnal IOP elevation conferred by trabeculectomy may be one of the key reasons trabeculectomy leads to slowed disease progression. While trabeculectomy may provide nocturnal control in patients at greatest risk for profound vision loss, the morbidity associated with filtration surgery suggests that a safer method to lower IOP at night remains a significant unmet need in glaucoma management.

The Rationale for Why Lowering Nocturnal IOP Elevation is Beneficial

While the evidence and rationale for decreasing nocturnal IOP to prevent glaucomatous progression is compelling, the reason why lowering IOP is an effective treatment for glaucoma is not fully elucidated. Early landmark studies demonstrated that high IOP slows axonal transport with irreversible damage starting at 4 hours. An early and important study by Quigley[56] in primates demonstrated that both acutely or chronically raising the IOP slowed or halted axonal transport in the optic nerve at the level of the lamina cribrosa. However, normalization of the IOP following 4 hours of IOP elevation allowed for the resumption of axonal transport without any permanent insult to the retinal ganglion cells (RGC). When axonal transport is disrupted for an extended period, apoptotic signals start an irreversible cascade leading to RGC deaths, the hallmark of damage in glaucoma. An additional study by Johansson[57] reported similar findings and found that axonal transport was completely restored without permanent damage after a transient IOP elevation to 50 mmHg for 2 hours was returned to baseline (IOP 15 mmHg). These studies support the idea that periodic IOP reduction over a 24-hour course, especially at night when spikes are prevalent, may prevent permanent optic nerve damage.

Recent research suggests that the underlying reason for IOP-induced axonal transport shutdown may lie with translaminar pressure difference (TLPD), the difference between IOP and intracranial pressure (ICP). When IOP is higher than ICP, the elevated TLPD increases stress and strain on the lamina cribrosa. In contrast, a decrease in IOP relative to ICP decreases the TLPD and therefore lowers strain on the lamina cribrosa. This mechanical stress on the lamina cribrosa may be what halts axonal transport. A study by Zhang[41] demonstrated that short-term ICP reduction, and therefore increased TLPD, disrupted axonal transport. This was successfully reversed after normalization of the TLPD, supporting the pathogenic impact of low ICP to RGCs. Additional studies have explored the effects of an increased TLPD, either due to a reduction of ICP or elevated IOP, on glaucomatous optic neuropathy. A low ICP, even in the setting of normal IOP, has been demonstrated to have an important role in the pathogenesis of glaucoma, especially those with NTG.[58–65] Collectively, these studies show that normalization of an increased TLPD, which is linked to progression, within a short time frame, allows for the resumption of axonal transport and clearance of toxic metabolites.[66] This suggests that periodic normalization of TLPD, especially at times most likely to have IOP spikes, can preserve ONH health, maintain RGCs, and prevent the apoptotic signaling cascade.

It is also important to consider the impact of the TLPD on blood flow and OPP, which may also contribute to glaucomatous damage. Zhang[41] demonstrated that the combination of low ICP and reduced OPP damages the RGCs more than either alone. Further, Siaudvytyte[67] compared neuroretinal rim area and blood flow behind the optic nerve in patients with NTG. In this study, lower ICP was correlated with NTG and patients with ICP <8.3 mmHg had significantly lower blood flow through the ophthalmic artery than patients with ICP >8.3 mmHg, suggesting that reduced ICP could also be linked to poor blood supply at the ONH. Thus, given the concern of nocturnal systemic hypotension and the importance of ocular perfusion, lowering IOP at night promotes increased ONH blood flow at a vulnerable period for patients.

Overall, the aggregation of clinical data has shown a connection between elevated nocturnal IOP and glaucoma, including NTG. Moreover, existing clinical and scientific literature supports the notion that reducing IOP, even periodically at night, can mitigate RGC death. In summary, these findings strongly support the advantages of lowering nocturnal IOP.

Therapies That Lower Nocturnal IOP

The evidence supporting the importance of lowering nocturnal IOP and minimizing IOP elevations throughout the 24-hour period is robust. However, the current landscape shows a very limited number of interventions that successfully minimize nocturnal IOP elevations in patients with glaucoma.

Until recently, only trabeculectomies have been shown to lower reliably lower nocturnal IOP. The Ocular Pressure Adjusting Pump (Balance Ophthalmics, Sioux Falls, SD, USA), is the only FDA-approved device that has been shown to lower nocturnal IOP.[68–71] While the device is worn, it lowers IOP by applying negative pressure independently to each periorbital region using a pressure-modulating pump and a pair of pressure-sensing goggles. The IOP-lowering effect of the device has been demonstrated in multiple studies, including a study by Goldberg in which mean nocturnal IOP was reduced by 35% during device usage.[68,72] Additional studies have demonstrated the benefits of device use on ocular blood flow. A recent study by Kamalipour[73] investigated changes in circumpapillary microvasculature using OCT-A, demonstrating a dose-dependent increase in retinal microcirculation corresponding to increased levels of negative pressure (ie −10, −15, −20 mmHg). Computational modeling demonstrated a significant reduction in biomechanical strain at the ONH, supporting the biomechanical benefit of employing negative periocular pressure to lower IOP.[74] The IOP lowering effect of the device was independent of baseline IOP or additional treatment.

Conclusion

Reduction of IOP during both day and night clearly provides a therapeutic benefit in slowing the progression of OAG, especially the difficult-to-treat NTG. This paper summarizes the findings of recent research to highlight the importance of nocturnal IOP control and the likely benefit of periodic IOP reduction in slowing the progression of glaucoma. The Ocular Pressure Adjusting Pump may be the first safe and effective method for reducing nocturnal IOP, especially for patients with NTG.

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