Original Article

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Diurnal Intraocular Pressure and Blood Pressure with Two Dosing Regimens of Brimonidine in Normal Tension Glaucoma

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Background. To compare the effects of 2 dosing regimens of brimonidine tartrate 0.2% on diurnal intraocular pressure (IOP) and systemic hemodynamics in patients with normal-tension glaucoma (NTG).

Methods. Twenty NTG patients were enrolled and randomized to receive either brimonidine twice daily (BID) for 4 weeks followed by brimonidine 3 times daily (TID) for another 4 weeks, or in reverse order. Diurnal variations of IOP and ocular perfusion pressure (OPP), as well as the 24-hour ambulatory blood pressure (BP) and pulse rate, were evaluated at baseline and after treatment. Baseline and post-treatment data were compared using a paired Student's *t* test, and treatment effects were compared between regimens using a crossover-designed analysis of variance.

Results. Both regimens decreased the mean ($p < 0.001$) and minimum ($p < 0.001$) diurnal IOP, and only the TID regimen decreased the maximum IOP with a marginal significance ($p = 0.049$). The TID regimen decreased the maximum OPP ($p = 0.009$) while the BID regimen caused no changes in OPP. No significant difference in IOP or OPP was noted between regimens at each time point. Neither regimen caused changes in BP or pulse rate as assessed using the 24-hour ambulatory monitoring device.

Conclusions. The TID regimen of brimonidine produces similar reductions in diurnal IOP for NTG patients as the BID regimen, and it alone decreases the maximum OPP. Neither of the 2 regimens causes exaggerated nocturnal reduction of BP.

Intraocular pressure (IOP) is an important risk factor of glaucoma and IOP-lowering therapy is beneficial in halting glaucomatous visual field deterioration, including that of normal-tension glaucoma (NTG).[1-3] Some patients, however, experience progressive optic nerve damage with apparently well-controlled IOP due to undetected high IOP; circulation impairment of the optic disc; and/or irreversible events of nerve degeneration.[4-10] Some ocular hypotensive medications currently on market have shown to reduce ocular blood perfusion and exaggerate the nocturnal systemic hypotension, thereby unfavorably influence the disease outcome.[11] This underlines the importance of taking all advantages and disadvantages of each glaucoma medication into account while treating glaucoma patients.

Brimonidine tartrate (Alphagan®; Allergan Inc, Irvine, CA, USA) is a selective α_2-adrenoreceptor agonist with a peak ocular hypotensive effect comparable to that of timolol.[12,13] It is appealing due to its neuroprotective effect on retinal ganglion cells, which has been demonstrated in some experimental models.[14,15] Several studies show that brimonidine 0.2% causes a statistically significant decrease in blood pressure (BP) and heart rate not associated with clinical symptoms.[12,13,16,17] However, ambulatory blood pressure monitoring (ABPM) that demonstrates a full 24-hour BP profile after brimonidine therapy has never been reported, although it is important for a glaucoma medication with vasoactive potential since nocturnal hypotension has been implicated as a contributing factor to glaucoma progression.[11,18]

Compared with latanoprost, brimonidine twice daily (BID) produces a comparable peak hypotensive effect on NTG, but the mean diurnal IOP is higher due to larger diurnal fluctuations.[19] Since controversy exists regarding the optimal dosing frequency of brimonidine in primary open angle glaucoma (POAG) and ocular hyperten-

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sion,[20,21] it is intriguing to ascertain whether brimonidine given 3 times daily (TID) can achieve a lower mean diurnal IOP with less diurnal fluctuations than the BID regimen. In this study, we compared the diurnal changes of IOP and ocular perfusion pressure (OPP), as well as the 24-hour profile of BP and pulse rate between the 2 regimens of brimonidine on NTG patients.

METHODS

NTG patients who had not received prior glaucoma therapy were recruited consecutively from the Glaucoma Service. Diagnosis of NTG was based on reproducible visual field defects of a retinal nerve fiber layer type, corresponding optic disc excavation, normal open angles, and multiple readings of untreated IOP on different occasions indicating values < 22 mm Hg. Perimetry was performed using program 24-2 of the Humphrey Field Analyzer 750 (Humphrey Instruments, San Leandro, CA, USA). A minimal field defect consists of a cluster of 3 adjacent points within 1 hemifield depressed by 5 dB or more from normal age values, with 1 of them depressed by at least 10 dB. Exclusion criteria were corneal abnormalities or any condition that prevented reliable applanation tonometry, other disorders that might cause visual field defects, history of ocular trauma/use of steroid, ocular surgery within 12 months of enrollment, ocular infection or inflammation within 3 months, concurrent use of monoamine oxidase inhibitors, or severe systemic diseases. If both eyes were eligible, the eye with more advanced field defects was selected. Institutional review board approval was obtained, and verbal and written consent was obtained from all subjects.

After baseline examination, patients were randomly allocated to receive either brimonidine BID for 4 weeks followed by brimonidine TID for another 4 weeks, or in reverse order. For diurnal measurement of IOP and OPP, the patients were hospitalized at baseline and at the end of each treatment period. At admission, corrected visual acuity, slit-lamp biomicroscopy and fundoscopy were performed. Ocular and systemic side effects that occurred during the period were recorded. One ophthalmologist who was unaware of IOP history, study eye or treatment assignment performed the IOP measurement with the same Goldmann applanation tonometer at 2-hour intervals from 2 PM to 10 PM on the first day and from 6 AM to noon on the secondary day. Resting BP was measured with 1 sphygmomanometer just before the IOP was measured. OPP was calculated as (1/3 systolic BP + 2/3 diastolic BP) × 2/3 – IOP. Medical staff instilled eye drops at 6 AM and 6 PM for BID regimen and at 6 AM, 2 PM and 10 PM for TID regimen. Patients were instructed to close eyelids for 5 minutes after drop instillation and encouraged to continue their normal routines as much as possible within the hospital boundaries.

Besides, the 24-hour ABPM was performed at 30-minute intervals with the same ambulatory blood pressure monitor (Spacelabs Medical, Inc. Redmond, WA, USA) on all patients before treatment and after they had been treated with each regimen for 3 weeks or longer, when the patients were living at home with routine life schedule. Data with pulse pressures < 10 mmHg when the systolic BP was below 100 mmHg and pulse pressures < 10% of the systolic reading when the systolic BP was greater than 100 mmHg were rejected as unphysiologic outliers.[22] Diastolic BP values greater than 160 mmHg were also excluded.[22] We defined daytime as 6 AM to 9:59 PM and nighttime as 10 PM to 5:59 AM. Patients were divided into "dippers" or "non-dippers" based on the criteria that both the mean systolic and diastolic daytime BP fell by more than 10% at night.[23]

Data were analyzed using the statistical software Stata (Stata Corporation, College Station, TX). Baseline and post-treatment values were compared using a paired Student's *t* test for each regimen. Treatment effects were compared between regimens using a crossover-designed analysis of variance with dosing regimen, period, and their interaction as factors, and changes in IOP, OPP, BP or pulse rate as the response. The proportion of dippers at baseline and with each regimen was compared with the McNemar's test. A p value less than 0.05 was considered statistically significant.

RESULTS

Data of IOP and OPP were obtained from 20 patients (6 females) who had completed both dosing regimen courses with a mean age of 59.3 ± 15.2 years. Analyses

of the ABPM data were performed on 17 of them. Three patients (15%) were excluded from that analysis because > 25% of the readings were either unsuccessful or deleted as outliers, which is consistent with prior use of the ABPM device.[22] There was no significant carry-over effect or period effect on IOP, OPP, BP, and pulse rate.

Both dosing regimens of brimonidine decreased the mean and minimum diurnal IOP from the baseline levels (all $p < 0.001$), and only the TID regimen decreased the maximum IOP with a marginal significance ($p = 0.049$) (Table 1). The TID regimen decreased the maximum OPP ($p = 0.009$) while the BID regimen caused no

Table 1. Intraocular pressure and ocular perfusion pressure at baseline and after brimonidine monotherapy

	Baseline	BID	TID	BID vs Baseline	TID vs Baseline	BID vs TID
Intraocular pressure (mmHg)						
maximum	16.6 ± 3.7	16.0 ± 3.4	15.7 ± 3.0	$p = 0.134$	$p = 0.049$	$p = 0.472$
minimum	12.0 ± 3.1	10.1 ± 2.6	10.4 ± 2.8	$p < 0.001$	$p < 0.001$	$p = 0.447$
mean	14.3 ± 3.2	13.0 ± 3.0	13.0 ± 2.9	$p < 0.001$	$p < 0.001$	$p = 0.868$
Ocular perfusion pressure (mmHg)						
maximum	54.7 ± 8.4	53.6 ± 8.6	51.1 ± 7.9	$p = 0.450$	$p = 0.009$	$p = 0.183$
minimum	41.6 ± 8.1	40.6 ± 7.7	40.2 ± 7.6	$p = 0.341$	$p = 0.164$	$p = 0.779$
mean	47.1 ± 7.6	47.6 ± 7.6	46.1 ± 7.3	$p = 0.650$	$p = 0.231$	$p = 0.249$

BID = twice daily dosing of brimonidine; TID = three times daily dosing of brimonidine.

Table 2. Blood pressure at baseline and after brimonidine monotherapy

	Baseline	BID	TID
Daytime			
Systolic blood pressure (mmHg)			
Maximum	143.7 ± 15.2	146.9 ± 19.3	141.2 ± 15.1
Minimum	94.9 ± 14.1	96.9 ± 14.1	94.8 ± 13.7
Mean	120.3 ± 12.2	121.6 ± 13.8	119.0 ± 11.0
Diastolic blood pressure (mmHg)			
Maximum	91.4 ± 11.3	96.5 ± 10.6	90.3 ± 12.3
Minimum	56.5 ± 10.6	57.5 ± 11.0	54.7 ± 9.7
Mean	74.4 ± 9.5	76.0 ± 10.3	74.3 ± 10.2
Pulse rate (beat/min)			
Maximum	92.2 ± 13.1	95.1 ± 17.8	96.2 ± 18.1
Minimum	56.9 ± 9.7	58.9 ± 8.0	58.1 ± 8.1
Mean	72.3 ± 11.5	74.6 ± 11.9	74.5 ± 9.7
Nighttime			
Systolic blood pressure (mmHg)			
Maximum	129.6 ± 16.9	128.9 ± 18.4	129.6 ± 17.3
Minimum	95.2 ± 13.5	88.5 ± 17.4	94.4 ± 14.3
Mean	111.3 ± 14.1	110.8 ± 14.3	111.7 ± 13.5
Diastolic blood pressure (mmHg)			
Maximum	81.5 ± 11.5	84.5 ± 11.8	82.8 ± 11.6
Minimum	56.7 ± 10.4	54.8 ± 10.2	58.1 ± 10.0
Mean	69.3 ± 9.5	69.0 ± 9.6	69.8 ± 10.1
Pulse rate (beat/min)			
Maximum	76.6 ± 12.8	75.1 ± 14.3	77.5 ± 13.8
Minimum	56.1 ± 8.7	54.6 ± 7.0	55.6 ± 10.0
Mean	63.7 ± 10.4	62.5 ± 8.5	63.3 ± 10.8

BID = twice daily dosing of brimonidine; TID = three times daily dosing of brimonidine.

changes in the mean, maximum, and minimum OPP (Table 1). No significant between-regimen differences were noted in the mean, maximum and minimum values of diurnal IOP or OPP (Table 1).

Fig. 1 shows that the BID regimen decreased the IOP significantly at 8 AM ($p < 0.001$), 10 AM ($p = 0.001$), 6 PM ($p = 0.033$), 8 PM ($p < 0.001$), and 10 PM ($p < 0.001$) while the TID regimen decreased the IOP significantly at 8 AM ($p < 0.001$), 10 AM ($p = 0.010$), 2 PM ($p = 0.038$), 4 PM ($p = 0.002$), 6 PM ($p = 0.005$), 8 PM ($p = 0.014$), and 10 PM ($p = 0.006$). Fig. 2 shows that the OPP at each time point did not change significantly after brimonidine therapy other than a decrease at 10 PM ($p = 0.005$) with the TID regimen. There was no significant between-regimen difference in IOP or OPP at each time point.

With the 24-hour ABPM, no significant changes in BP or pulse rate were noted with either regimen except that the maximum daytime diastolic BP was higher with the BID regimen than that at baseline ($p = 0.026$) and with the TID regimen ($p = 0.016$) (Table 2). There was

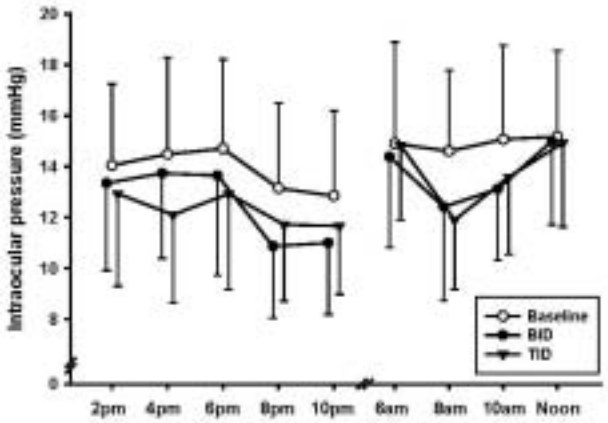

Fig. 1. Diurnal intraocular pressure at baseline and after treatment with twice daily (BID) or 3 times daily (TID) dosing frequency of brimonidine.

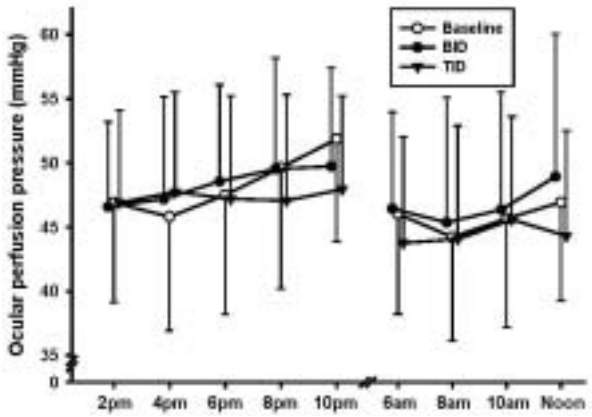

Fig. 2. Diurnal ocular perfusion pressure at baseline and after treatment with twice daily (BID) or 3 times daily (TID) dosing frequency of brimonidine.

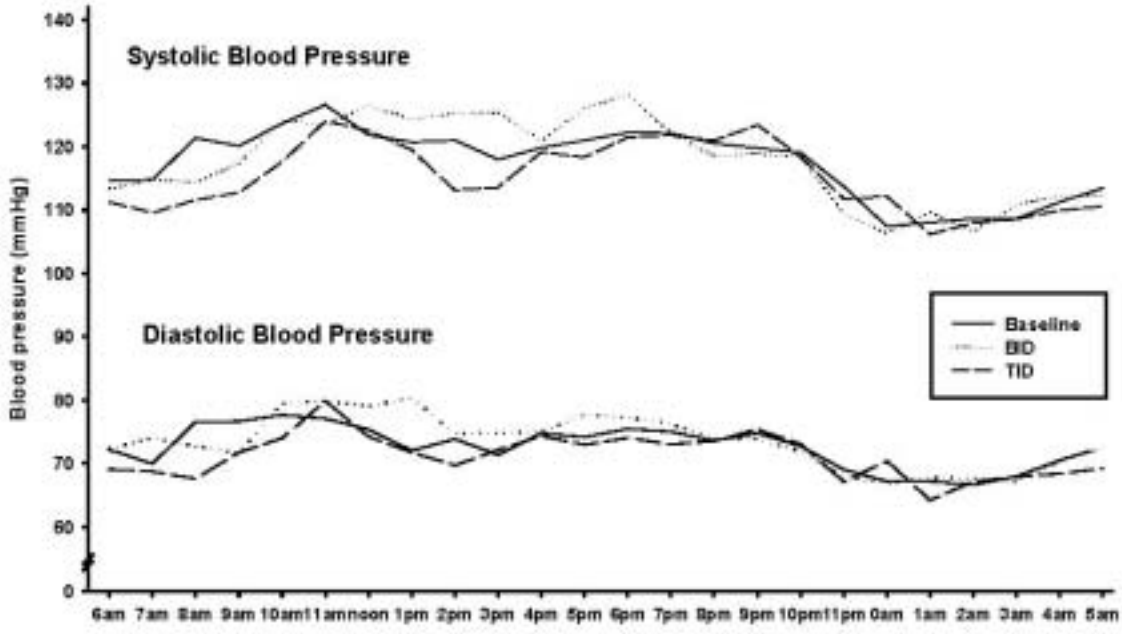

Fig. 3. The 24-hour systolic and diastolic blood pressure at baseline and after treatment with twice daily (BID) or 3 times daily (TID) dosing frequency of brimonidine.

no significant difference in the hourly average BP between regimens (Fig. 3). The proportion of dippers remains similar after treatment with either regimen (both $p = 0.317$).

No significant ocular or systemic side effects were encountered. Seven patients were under concurrent systemic cardiovascular medication (β-blockers in 3 patients, calcium channel blockers in 4 patients, and angiotensin-converting enzyme inhibitors in 1 patient), and all kept using the same medication during the study.

DISCUSSION

We demonstrate that both regimens of brimonidine decrease the mean and minimum diurnal IOP and they produce a similar reduction in IOP at each measured time point. The TID regimen reduces the maximum diurnal OPP, while the BID regimen does not affect OPP significantly. The physiological nocturnal decrease in BP is not exaggerated after brimonidine therapy.

Accumulating evidence suggests that optimal control of IOP over the 24-hour period is important in minimizing the risk of progressive optic nerve damage in glaucoma.[5,6] Zeimer *et al* have shown that patients with progressive field loss have more frequent IOP peaks than patients with stable fields.[5] In a succeeding study, they found that large fluctuations in IOP were not only associated with an enhanced risk for progression but had an effect over other strong risk factors.[6] We found that although both regimens of brimonidine reduced the mean and minimum diurnal IOP, only the TID regimen reduced the maximum IOP to a degree of marginal significance. Thus, brimonidine reduced the mean IOP with increased diurnal fluctuations. The clinical significance of this apparently paradoxical finding remains to be determined.

The IOP measured at 6 AM and noon was almost unaltered with brimonidine therapy (Fig. 1). It seems that the hypotensive effect of brimonidine is not potent enough 6 hours following application to reduce the IOP on the plateau of the diurnal curve. The between-regimen difference in IOP was biggest 2 hours following the afternoon dose of TID regimen (4 PM), with a difference short of statistical significance ($p = 0.051$). Therefore, increasing the dosing frequency of brimonidine is not helpful in reducing the mean IOP and dampening the diurnal fluctuations. One dosing frequency study of brimonidine on patients with POAG or ocular hypertension has similar findings.[20]

There is a growing consensus, albeit not proved, that the difference between BP and IOP may be more important than the IOP itself in the pathophysiology of glaucomatous optic neuropathy. In susceptible patients, a lower OPP is associated with reduced end diastolic blood velocity and increased vascular resistance in both the ophthalmic artery and central retinal artery.[24] Previous studies did not find adverse effects on ocular hemodynamics with brimonidine therapy.[25-27] In this study, the TID regimen decreased the maximum diurnal OPP (-3.6 mmHg, $p = 0.009$) while the BID regimen caused no changes in OPP. It is hard to right away ascertain the impact of such a decrease in maximum OPP. Since the TID regimen decreased the maximum IOP only with borderline significance, and no significant difference in IOP or OPP could be found at each time point between the 2 dosing regimens, we conclude that TID dosing of brimonidine is not more beneficial than the BID dosing to NTG patients.

The nocturnal decrease of BP is physiologically related to the reduced sympathetic tone and increased vagal tone during sleep.[28,29] The absence of it is associated with complications of hypertension.[29,30] Conversely, exaggerated nocturnal hypotension may yield inadequate tissue perfusion in susceptible patients.[30] Graham and Drance have shown that glaucoma patients with field progression have lower nocturnal BP variables than patients with stable fields.[18,22] Hayreh and associates reported that patients using beta-blocker eye drops experience a greater drop in nocturnal diastolic BP.[11] Furthermore, NTG eyes receiving beta-blockers show visual field progression more often than those not receiving beta-blockers.[11] With ABPM, we found no changes in BP or pulse rate during daytime and nighttime hours with either regimen of brimonidine. Pressure readings taken by the ABPM device correlate well with intraarterial measurements.[31] It is a well-established procedure that demonstrates BP in the patient's natural environment during different levels of physical activity and mental stress. Sleep disturbance with ABPM is minimal if the frequency of cuff inflation is between 15 and 30 min-

utes.[28,29,31]

The present study is limited by the issue of compliance and by its small sample size. Having the medical staff instill eye drops during the period of hospitalization lessens the bias resulting from patient incompliance of diurnal IOP and OPP data. The results of similar diurnal IOP variations between regimens are in accordance with 1 study on 101 patients with POAG or ocular hypertension.[20] This suggests that the conclusion of our study might not be affected significantly by its small sample size. Seven patients were under concurrent systemic cardiovascular medication that may influence the evaluation of OPP. However, while comparing the data of the patients with and without such medication, no significant difference was identified, either at baseline or after brimonidine therapy, in IOP and OPP regarding the maximum, minimum, and mean values. Besides, including patients with cardiovascular disease using concurrent medication reflects the practice pattern in real life, since many glaucoma patients are elderly people suffering from such disease.[32] This study is also limited by the lack of IOP and OPP data between midnight and 6 AM.

In conclusion, brimonidine lowers IOP without altering the nocturnal decrease in BP or pulse rate. In treating NTG patients, the TID regimen of brimonidine is not able to achieve a lower IOP with less diurnal fluctuations than the BID regimen.

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