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ORIGINAL RESEARCH

Effect of systemic antihypertensives on change in intraocular pressure after initiating topical prostaglandins for primary open-angle glaucoma

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Purpose: There is a limited understanding of factors that influence the efficacy of topical glaucoma medication. Our study is a long-term, case–control analysis of how systemic antihypertensive (anti-HTN) medications influence the change in IOP after initiating prostaglandin (PG) drop therapy.

Materials and methods: A retrospective chart review of 3,781 patients was performed on patients with a diagnosis of glaucoma suspect that progressed to primary open-angle glaucoma (POAG) by ICD-9 codes over a 10-year period. Inclusion criteria consisted of the following: 1) progression from preglaucoma to glaucoma diagnosis in a time span of ≥6 months; 2) two visual fields recorded between these dates; 3) initial average IOP of both eyes of ≥21 mmHg; and 4) initiation of topical PG therapy alone. IOP (in mmHg) was measured at initiation of PG drops and at next visit.

Results: One hundred eleven patients were qualified for analysis. Patients not on anti-HTN agents had an average IOP decrease of 6.38±0.56 mmHg. Comparatively, patients on anti-HTN agents had an average IOP decrease of 6.66±0.48 mmHg (P=0.61). In addition, there was no statistical difference between IOP decrease between patients on single vs multiple systemic anti-HTN agents (P=0.85). There were eight nonresponders to PGs on no anti-HTN medications and 12 nonresponders on anti-HTN medication (P=0.55).

Conclusion: Systemic anti-HTN medication use did not significantly impact IOP reduction after topical PG initiation for POAG. Additionally, nonresponse to PG therapy was not correlated to systemic anti-HTN use.

Keywords: glaucoma, topical prostaglandins, IOP, systemic antihypertensives, ocular hypertension, prostaglandin eye drops

Introduction

Glaucoma, one of the leading causes of blindness in the world, is a disease in which damage to the optic nerve occurs due to increased IOP secondary to either increased production of aqueous humor or decreased outflow of aqueous humor. Glaucoma has many subclassifications including closed-angle glaucoma, neovascular glaucoma, and primary open-angle glaucoma (POAG). POAG is the most common type of glaucoma in the USA.[1,2]

POAG is generally treated with topical eye drops such as alpha-2 agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandins (PGs). Beta-blockers, alpha-2 agonists, and carbonic anhydrase inhibitors work by decreasing aqueous humor secretion into the anterior chamber of the eye. PGs increase aqueous drainage by increasing outflow through the scleral canal. Patients with glaucoma commonly have other chronic comorbid conditions, notably hypertension, diabetes, and migraines,

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which also happen to be risk factors. PGs are first-line agents in treating POAG since they have shown the highest efficacy in decreasing IOP.[2–4]

Recent studies have examined the effects of systemic antihypertensive beta-blocker therapy administered concurrently with topical beta-blocker glaucoma therapy and have identified a smaller decrease in IOP compared with topical beta-blocker therapy alone. Concurrent treatment with systemic antihypertensive beta-blocker therapy has also been shown to augment the efficacy of brimonidine, an alpha 2 agonist, in lowering IOP.[3,5,6] These findings suggest that certain systemic antihypertensive agents may have either a synergistic or antagonistic effects with certain kinds of topical glaucoma therapy.

There is currently a limited understanding of which factors influence the efficacy of topical PG medication in patients with POAG. This study was designed to identify the relationship between the use of different systemic antihypertensive medications and the subsequent change in IOP when initiating topical PG therapy in patients with newly diagnosed POAG. Although current literature has described some ways in which systemic antihypertensive medications affect the progression of glaucoma, there is very limited information about how these medications influence the efficacy, or magnitude of decrease in IOP, of topical PG therapy.[6–9] A better understanding of these interactions would be a valuable supplement to clinical decision making, efficiency, and time management, as well as disease treatment and overall outcomes.[10–15]

Materials and methods

A retrospective chart review of 3,781 patients was performed on patients with a diagnosis of glaucoma suspect that progressed to open-angle glaucoma by ICD-9 codes over a 10-year period. This retrospective review was approved by Specialty Surgery Center IRB prior to the start of the study. The patient data were gathered using the electronic medical record at Medical Center Ophthalmology Associates in San Antonio, Texas, USA. All patients signed a consent form that allowed their protected health information to be used. All stages of this study were conducted in accordance with the principles set forth by the Declaration of Helsinki. Criteria for inclusion in this study were as follows: 1) a patient must have an initial IOP of ≥21 mmHg measured with Tono-Pen AVIA tonometer before initiation of topical PG medication; 2) treatment for POAG should consists of topical PG therapy alone; 3) patients must have demonstrated progression from glaucoma suspect to diagnosis of POAG according ICD-9 codes on chart review over a span of 6 months or longer; 4) the patient must have at least two visual field tests on record between the time of glaucoma suspect diagnosis and POAG diagnosis. The rationale for this last criterion was to further support correct diagnosis of POAG. Diagnosis of POAG was made clinically with the help of a combination of optical coherence tomography (OCT), tonometry, visual field, and fundus examination. The topical PG prescribed to treat POAG in the patient population studied at our institution is latanoprost 0.005% (50 mg/mL) daily. These inclusion criteria were implemented to give more legitimacy to our results by ensuring patients were properly worked up in the same clinic with visual field testing, were being followed chronically and consistently for progression of glaucoma suspect to POAG, and by keeping an IOP cutoff consistent with commonly accepted IOP cutoff for POAG diagnosis.[16,17]

Patient charts that met inclusion criteria were evaluated for demographic data, diagnosis of hypertension, systemic antihypertensive medications, and IOP measurements (mmHg) at the initiation date of topical PG therapy for POAG. IOP at the subsequent visit following initiation of therapy was then recorded. The difference in IOPs at the dates of treatment initiation and at the subsequent visits was used to calculate average change in IOP. Antihypertensive medications were reviewed at the time of initiating PG drop and subsequent visit to control consistency in blood pressure control and were included if there was no change in medications. Data were evaluated to compare average change in IOP between patients on no systemic antihypertensive medications, single systemic antihypertensive therapy, and multiple systemic antihypertensives. A paired *t*-test was used to evaluate for significant change in IOP between these three groups.

Results

One hundred and eleven patients met the inclusion criteria for analysis. The average IOP drop after initiating PG therapy was 6.60 mmHg. Our demographic breakdown was composed of 43.2% males and 56.8% females. Of that group, 58.6% were Caucasian, 34.2% were Hispanic, and 7.2% were of another ethnicity. In this population, 59.5% of patients had a previous diagnosis of hypertension, while 40.5% did not. The age range of our patient population was 38–94 years (median =70, mean =68.7) (Table 1).

Once PG therapy was initiated, patients not on antihypertensive agents (N=40) had an average IOP decrease of 6.38± 0.56 mmHg, while patients on single antihypertensive agents (N=40) had an average IOP decrease of 6.66±0.48 mmHg.

Table 1 Patient demographic data broken down by gender, ethnicity, hypertension diagnosis, and age

Patient demographics (N=111)	
Characteristics	N (%)
Gender	
Male	48 (43)
Female	63 (57)
Ethnicity	
Caucasian	65 (59)
Hispanic	38 (34)
Others	8 (7)
Hypertension diagnosis	
Yes	71 (64)
No	40 (36)
Age (years)	
Median	70
Range	38–94

Patients on multiple antihypertensive agents (N=31) had an average IOP decrease of 6.82±.68 mmHg (Table 2).

There was no significant difference between the magnitude of IOP decrease between patients on no systemic antihypertensive medications vs a single antihypertensive medication (P=0.61). In addition, there was no statistical difference between IOP decrease when comparing patients on single vs multiple systemic antihypertensive agents (P=0.85; Table 3).

In addition, we compared IOP decrease in terms of class of antihypertensives. No significant difference was found in IOP decrease in all these groups.

The number of nonresponders (IOP reduction <10%) to PG drops was split with eight patients in the group not on antihypertensive medications and 12 patients in the group who were taking systemic antihypertensives. A chi-squared analysis between these two groups showed no significant difference between proportion of nonresponders in patients on antihypertensives and patient who were not (P=0.55).

Discussion

The relationship between hypertension and glaucoma remains unclear. Several studies have found that systemic hypertension, vasospasm, and acute hypotension are potential risk factors for glaucoma,[18–22] while other studies have found no association between hypertension and OAG.[23,24] In a study by Klein et al, blood pressure and IOP levels were shown to be correlated and IOP levels are a risk factor for developing glaucoma in most populations.[25] When it comes to treatment, IOP is the only modifiable factor in POAG.[26] Logically, it seems that by lowering a patient's blood pressure, the IOP should decrease and the rate of glaucomatous damage reduce as well; however, the relationship between blood pressure and glaucoma progression is confounded by its effect on IOP. This along with other mechanisms may explain why many conflicting studies exist on the influence that blood pressure-lowering agents have on glaucoma progression. For instance, taking antihypertensives at night may worsen glaucoma because both the antihypertensives and a person's circadian rhythm contribute to lowering of blood pressure to a level where ischemia in ocular blood vessels can occur.[27] Taking these factors into consideration, it is unclear how much of a role antihypertensives play in glaucoma progression.

PGs are used to treat glaucoma because they effectively lower IOP with simple dosing and limited side effects.[28] By lowering the IOP of the eye, PGs help to slow or inhibit further damage to the optic nerve caused by high pressures in the

Table 2 Comparison of mean decrease in IOP following prostaglandin drop therapy isolating different classes of antihypertensive medications

Antihypertensive class	Number of patients taking drug	Baseline IOP (mean±SE, mmHg)	IOP decrease from baseline IOP (mean±SE, mmHg)	Mean percentage reduction from baseline IOP (mean±SE)
No drugs	40	23.724±0.445	6.566±0.572	27.2±2.0
ACE inhibitors	30	23.767±0.413	6.250±0.568	25.8±2.1
ARB	26	23.712±0.478	6.712±0.687	28.0±2.7
BB	17	23.088±0.410	6.500±0.881	27.6±3.4
Thiazides	15	24.333±0.654	7.467±0.919	30.2±3.4
CCB	16	23.813±0.559	7.188±1.113	29.5±4.5
Loop diuretic	4	22.750±1.109	9.250±2.454	39.8±9.0

Notes: The majority of these patients were on multiple antihypertensive medications of different classes. No statistical difference was found in mean IOP decrease between different antihypertensive drug classes.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; SE, standard error.

Table 3 No statistically significant difference was found in IOP decrease following starting topical prostaglandins with regard to the number of different antihypertensive drug classes the patients were taking at the initiation of prostaglandin drop therapy

Change in IOP after initiating prostaglandin therapy				
Medication regimen	**Average pretreatment IOP (mmHg, both eyes)**	**Average posttreatment IOP (mmHg, both eyes)**	**Average decrease in IOP**	***P*-value**
No systemic antihypertensive medications	23.72	17.39	6.34	0.61
Any systemic antihypertensive medications	23.72	17.02	6.70	
Single systemic antihypertensive medications	23.79	17.19	6.60	0.85
≥2 systemic antihypertensive medications	23.63	16.81	8.82	

eye. With contradictory reports on the efficacy of IOP reduction in systemic antihypertensives, and with the existence of people who are poor responders to PG therapy,[29] this study was able to look at any differences that may exist between patients on PGs solely and those also on antihypertensives. Other studies have looked at outcomes in patients taking both systemic medications and PGAs. A Canadian study found that patients who were taking antihypertensives while on PGAs were less likely to need additional drop therapy compared with patients just taking PGAs. This suggests a possible synergistic effect in glaucoma treatment between topical PGs and systemic medications.[30] The report did not look at IOP reduction directly like in our study, but instead looked for the need for adjunctive drop therapy as a proxy for glaucoma progression; however, the reasons for why an adjunctive IOP reducing drop was added were not detailed in the study. Because our study looked directly at magnitude of IOP reduction when systemic antihypertensives are taken along with PG, our results show that antihypertensives are unlikely to influence the efficacy of PGAs. By eliminating variables such as concurrent medication use, we can better understand which factors truly affect the efficacy of topical PG drops.

A recent study published in the American Academy of Ophthalmology (AAO) found that certain systemic medications influenced the progression of POAG. The AAO paper studied the relationship between systemic medications and the likelihood of a required procedure for POAG. It was found that three separate medication classes had statistically significant results.[9] Systemic beta-blockers were found to have a protective effect on POAG; thus, patients on these medications required fewer procedures. It has long been known that systemic beta-blockers can lower IOP, and thus, these medications may provide some benefit to disease progression.[3,6] It has also been shown that systemic medications like beta-blockers can impact the efficacy of topical drop medications such as timolol which are used to lower IOP.[3] The study also found that Selective serotonin reuptake inhibitors (SSRIs) may have a protective benefit in POAG progression. Patients on SSRIs were 30% less likely to require a procedure pertaining to POAG than nonusers of SSRI.[9] On the contrary, calcium channel blockers (CCBs) were shown to actually increase progression to POAG and these patients required more ocular procedures than patients not on CCBs. According to this study, patients on CCB were 26% more likely to require a procedure due to their POAG than patients not on CCBs.[9]

Studies such as these are very intriguing and open up the possibilities of systemic medication affecting progression of POAG. While these studies are finding interesting correlations, there have been no studies showing adequate explanations for these findings. Furthermore, there are certain weaknesses to these studies mentioned because it is not known what variables each ophthalmologist is looking at when deciding surgical management. There is lack of uniformity between each ophthalmologist's decision making that can lead to skewed results. This is where our project can add value to these unexplained findings. If ophthalmologists are deciding to move forward with procedures based on IOP readings, our research shows that systemic antihypertensive use will not falsely alter IOP readings in patients on PG drops. Currently, there is very little knowledge of factors influencing PG therapy. Our study shows that systemic antihypertensive medications do not alter the IOP reduction between patients taking antihypertensives and patients not taking any antihypertensives. Our study also shows that there is no alteration in IOP reduction between patients taking one antihypertensive versus taking multiple antihypertensives. This study allows us to eliminate certain variables from our decision making when we consider those that are influencing POAG progression. By showing that systemic antihypertensives have no

effect on IOP reduction in patients on PG therapy, it suggests that another pathologic process is at work in patients described in the AAO study. For instance, patients on CCB may have a higher risk of POAG progression, but this risk would not be attributed to the lack of efficacy of PG drops in reducing IOP.

An important circumstance we explored was patients not responding to PG therapy. It is not understood what contributes to a patient's nonresponse. It has been shown that ~15% of patients put on PG therapy are nonresponders.[28] There currently is no widely acceptable definition of nonresponders to PG drops; however, we looked at multiple studies that used <10% reduction in IOP as a cutoff for their nonresponders.[29,31] Going by this definition, we found that the number of nonresponders (IOP reduction <10%) to PG drops was split with eight patients (21%) in the group not on antihypertensive medications and 12 patients (15%) in the group that were taking systemic antihypertensives. Our data are consistent with studies we looked at which showed approximately a 14%–15% nonresponse rate in their patient population.[29] The fact that there was no statistically significant difference between the total number of nonresponders in the group of patients on antihypertensives versus the group of patients not taking antihypertensives means that nonresponse to PG drop therapy supports the notion that this phenomenon is independent of a medication interaction involving antihypertensives. This is important because a substantial number of patients (~15%) do not respond to PG therapy, which is the first-line treatment for lowering IOP.

Previous research has found that ophthalmologists spend 27% of each patient visit time entering information into the electronic health records (EHRs), equating to an average of 3.7 hours per day.[1] Research has shown that less time spent on EHR could result in improved clinical efficiency and improved patient satisfaction.[10–15] The implication of these results is that ophthalmologists may not need to worry about the effects of different antihypertensive medications on patients when prescribing PG therapy for the treatment of POAG. Alleviating concern about a patient's antihypertensive medications, ophthalmologists can prescribe PGs knowing that its efficacy or nonresponse is not attributed to the patient's concurrent antihypertensive use. In addition, primary care physicians who are prescribing antihypertensive medications do not have to worry about decreasing PG IOP-lowering effects.

For now, more research needs to be done in order to better understand the disease process of glaucoma. There are too many contradictions in the literature for us to be sure of what associations exist between systemic medications and glaucoma. Our study supports the notion that systemic antihypertensives did not affect the efficacy of topical PG drops and are not factors in patients who are nonresponders to PG.

Limitations

This study has limitations associated with monitoring diagnosis, treatment, and disease progression of POAG. For one, although the inclusion criteria attempted to ensure that all patients would be on a similar stage of POAG progression, there was variability in IOP at the time of diagnosis, which may allow for a wide range of posttreatment IOP. Additionally, the main indicator that was followed in this study to gauge the efficacy of glaucoma treatment was change in IOP. In reality, this is not as important of a marker of glaucoma disease state as OCT imaging or visual field testing. In addition, follow-up appointments for evaluation of efficacy of PG therapy occurred at variable time after diagnosis. Regarding assessing the effects of both systemic antihypertensive therapy and PG therapy, it is possible that noncompliance with either antihypertensives or PGs may have skewed results.

A study in AAO published in July 2018 showed negative effects of CCBs and positive effects of SSRIs on progression of POAG.[9] Our results did not show decreased effect of CCB on PG IOP-lowering effect. In addition, this was a single-center study that may have led to regional biases. Also, we did not account for patients on SSRIs or serotonin-norepinephrine reuptake inhibitors, which have been shown to alter progression of POAG in certain recently published studies.

Medical Center Ophthalmology Associates (MCOA) does not regularly record blood pressure values for their patients, so we were not able to correlate IOP with blood pressure. This is a limitation because some studies have shown that blood pressure can influence IOP.[25]

Finally, we did not distinguish between the different PG eye drops available. There is a debate on the difference in efficacy of different PG drops. One study showed that bimatoprost had more clinically significant IOP-lowering effect than tafluprost, latanoprost, and travaprost.[29,32] Another study showed no statistical difference in efficacy between drops.[33]

Conclusion

Systemic antihypertensive medication use did not affect the magnitude of IOP reduction in patients with newly diagnosed POAG who were treated with topical PG therapy. Additionally, nonresponse to PG therapy was not correlated to systemic antihypertensive use.

Data sharing statement

Data were gathered from MCOA Electronic Medical Records and due to patient confidentiality, are not publicly available.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Michael Singer is a consultant for Allergan, Allegro, Ampio, Genentech, Ophthotech, Regeneron, Santen, Aerpio, Optos, Alcon, Clearside, Notal Vision, Guidepoint, and Alimera. The other authors report no conflicts of interest in this work.

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