2012

Is Fixed-combination Prostaglandin Analog/β-blocker Therapy Safe and More Effective than β-blocker Monotherapy in the Prevention of Disease Progression in Adults with Open-angle Glaucoma?

My-Hang Pham
Philadelphia College of Osteopathic Medicine, MyHangPh@pcom.edu

Is fixed-combination prostaglandin analog/β-blocker therapy safe and more effective than β-blocker monotherapy in the prevention of disease progression in adults with open-angle glaucoma?

My-Hang Pham, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirement for

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2011

ABSTRACT

Objective – The objective of this selective EBM review is to determine whether fixed-combination prostaglandin analog/β-blocker therapy is safe and more effective than β-blocker monotherapy in the prevention of disease progression in adults with open-angle glaucoma.

Study Design – Review of three English language randomized controlled trials published in 2008 and 2010.

Data sources – 3 randomized, controlled, double-blind trials comparing fixed-combination prostaglandin analog/β-blocker therapy to β-blocker monotherapy were found using Pubmed, Medline, and Cochrane databases.

Outcome Measured – Disease progression/regression was assessed by post-baseline measurement of IOP during three follow-up visits throughout the trials. The safety profile of each therapy was assessed by monitoring the number of adverse events reported by the participants or observed by the researchers.

Results – All three studies demonstrated a significantly greater IOP reduction in participants treated with fixed combination prostaglandin analog/β-blocker therapy. There was a significantly higher incidence of adverse events in the fixed combination group compared to the β-blocker monotherapy group; however, the fixed combination therapy was determined to be well-tolerated and superior over β-blocker monotherapy in the prevention of disease progression of open-angle glaucoma.

Conclusions – Fixed combination prostaglandin analog/β-blocker therapy is safe and more effective than β-blocker monotherapy in the prevention of disease progression in adults with open-angle glaucoma. The simple dosing schedule increases patient adherence compared to the more complex multi-drug regimen of the individual active components.

Key Words – “open-angle glaucoma”, “combination therapy”, “prostaglandin analog”, “β-blocker”

INTRODUCTION

Open-angle glaucoma (OAG) is a progressive disease characterized by insidious optic nerve damage that is commonly attributed to chronic intraocular pressure (IOP) elevation.[1, 2] In this type of glaucoma, IOP elevation is due to impaired drainage of aqueous fluid through the trabecular meshwork to the anterior chamber. The exact mechanism of optic nerve damage by increased IOP is not yet understood.[1] However, chronically elevated IOP results in optic nerve atrophy and enlargement of cup-to-disc ratio, consequently leading to visual field impairment progressing to irreversible vision loss.[1,2]

Early detection and prompt treatment of OAG is important within the practice of physician assistants since glaucoma is one of the leading causes of preventable blindness in the United States.[1] Glaucoma affects more than two million Americans, accounting for an estimate of more than seven million office visits annually and $1.5 billion in direct healthcare cost.[3] The prevalence of OAG is highest in diabetic patients and those with affected first-degree relatives.[2] Chronic IOP elevation in OAG is often asymptomatic until severe optic nerve damage has already occurred and permanent visual impairment has ensued.[1,2] Therefore routine screening and early treatment of glaucoma are essential to halt the progression of the disease and to prevent irreversible visual loss.

The treatment of OAG and blindness prevention can be achieved through pharmacologic agents aimed at reducing the IOP by decreasing aqueous fluid production or increasing aqueous fluid outflow. Topical agents to suppress aqueous production include β-adrenergic blocking agents, alpha$_2$-adrenergic agonists and carbonic anhydrase inhibitors.[1,2] Agents that facilitate aqueous outflow include prostaglandin analogs and parasympathomimetic agents. Laser

trabeculoplasty and glaucoma drainage surgery (trabeculectomy) are effective treatments for patients with inadequate response to the less invasive medical treatments.[2]

Most patients with OAG respond well to medical treatments. Nonetheless, there are still a large number of patients who require more than one topical agent for adequate IOP control. Prostaglandin analogs and β-blockers are often first-line agents and may be used concurrently to maximize IOP reduction due to their different mechanisms of action.[2] However, the complexity of multi-drug regimen due to their different dosing schedule has made it a challenge to achieve satisfactory patient compliance.[4,5] Therefore, many formulations of fixed-combination prostaglandin analog/β-blocker have been developed to enhance patient adherence to effectively treat and prevent the progression of glaucoma.

OBJECTIVE

The objective of this selective EBM review is to determine whether fixed-combination prostaglandin analog/β-blocker therapy is safe and more effective than β-blocker monotherapy in the prevention of disease progression in adults with open-angle glaucoma.

METHODS

All three studies included in this selective EBM review were randomized, double-blind, controlled trials. The studied population included patients 18 years of age or older with open-angle glaucoma or ocular hypertension. The intervention used in the randomized controlled trials was fixed-combination prostaglandin analog/β-blocker therapy. The treatment group was compared to a comparison group in which patients only received β-blocker monotherapy.

The article search was performed by the author of this selective review using PubMed, MEDLINE, and Cochrane databases with keywords “open-angle glaucoma”, “combination therapy”, “prostaglandin analog”, and “β-blocker”. All three articles were published in English

in peer-reviewed journals. Inclusion criteria for the search were randomized controlled trials and publication date between 1996 to present. Exclusion criteria included systematic reviews, studies published prior to 1996, animal trials, and patients under 18 years of age. Table 1 outlined the demographics and characteristics of the included studies.

Table 1. Demographics and characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion criteria	W/D	Interventions
Higginbotham et al., 2010	RCT	394	≥ 18	- primary OAG or ocular HTN - Were receiving a β-blocker for ≥ 4 weeks before screening. - mean IOP between 26-36 mmHg - best-corrected visual acuity of 20/200 or better	- Angle-closure glaucoma - hx of ocular procedure, inflammation w/i 3 months or infection w/i 3 wks before screening - use a systemic med known to affect IOP - contraindicated to β-blocker - hypersensitivity to benzalkonium chloride - abnormal ocular conditions or uncontrolled systemic ds - women of childbearing potential w/o contraceptive methods or were pregnant/ nursing.	56	Fixed-combination latanoprost/timolol maleate vs. individual components
Varma et al., 2010	RCT	854	≥ 18	- primary OAG or ocular HTN - IOP ≥ 30 mmHg w/o ocular hypertensive meds or ≥ 25 mmHg with prior therapy	- Not specified	Not specified	fixed combination latanoprost/timolol vs. individual components
Brandt et al., 2008	RCT	1061	≥ 18	- ocular HTN, OAG, or angle-closure glaucoma, and who required B/L ocular hypotensive tx - best corrected visual acuity of 20/200 or better O.U. - IOP ≥ 24 mmHg	- uncontrolled systemic ds, significant ocular irritation, or active ocular ds - contraindications to tx w/ study meds or their components - conditions that precluded accurate IOP readings - surgery w/i the past 3 months - Concomitant ocular meds - Pregnant women or women of childbearing age w/o adequate contraceptive methods	74	fixed combination Bimatoprost/timolol vs. individual components

OUTCOMES MEASURED

The outcomes measured in all three RCTs include disease progression/regression and safety, which are both patient oriented evidence that mattered to the patients (POEMs). Since OAG is an asymptomatic and insidious condition, disease progression was defined as an increase in IOP and disease regression as a reduction in IOP. Lowering IOP halts optic nerve damage and prevents the progression of the disease to complete irreversible blindness. Several studies have proposed that long-term large diurnal IOP fluctuation may be associated with disease progression. Therefore Varna et al. also studied the effectiveness of fixed combination therapy on the reduction of diurnal IOP fluctuation.[6] Higginbotham et al. and Brandt et al. investigated the safety profile of the intervention by assessing the number overall reported adverse event and ocular-related adverse events.[4,5]

Brandt et al. and Higginbotham et al. scheduled follow-up IOP measurements at weeks 2, 6, and 12;[4,5] Varna et al. scheduled follow-up IOP measurements at weeks 2, 13, and 26.[6] The IOP for each participant in all three studies was measured at three different times during each follow-up visit. The diurnal IOP was the average of the three IOP measurements during each visit; and diurnal IOP fluctuation was the difference between the highest and lowest IOP of the three measurements taken at each visit.[4,5,6] Varna et al. also converted the diurnal IOP fluctuation into dichotomous data as high (> 6 mmHg) and low (< 6 mmHg).[6]

The safety profile of the intervention and comparison group was analyzed by monitoring the number of adverse events reported by the participants or observed by the researchers. The severity of the adverse event and whether it was treatment-related were also assessed by the researchers. Treatment-related adverse events were defined as those with onset or worsening after the initiation of the therapy.[4,5]

RESULTS

The study performed by Brandt et al. demonstrated statistically significant ($p < 0.001$) mean decreases from baseline IOP by the end of the trial of 8.1 $\pm$ 3.3 mmHg and 6.4 $\pm$ 3.5 mmHg for the fixed combination therapy and β-blocker monotherapy, respectively. The efficacy of the treatment was measured as a mean diurnal reduction greater than 20% from baseline IOP and IOP of less than 18 mmHg.[4] The percentage of participants achieving > 20% reduction from baseline IOP were 81.8% for the combination group and 49.8% for the β-blocker group; and the percentage of those with IOP < 18 mmHg were 39.2% and 12.2%, respectively (Table 2).[4] The number needed to treat based on the data on IOP reduction is 4.

Table 2. The efficacy and safety of each treatment group reported by Brandt et al.

	Efficacy		**Safety**
	> 20% reduction*	< 18 mmHg*	# treatment-related AEs*
Fixed combination	81.8 % (436/533)	39.2% (209/533)	41.5 % (221/533)
β-blocker monotherapy	49.8 % (131/263)	12.2 % (32/263)	24.7 % (65/263)

Number needed to treat: 4
* Between-group p value: $p < 0.001$

Higginbotham et al. reported statistically significant ($p < 0.001$) mean IOP differences (fixed combination – monotherapy) between the fixed combination group and the β-blocker group ranging from -3.79 mmHg to -2.14 mmHg. The baseline diurnal IOP values were similar between the two treatment groups; however, the postbaseline diurnal IOP values at weeks 6 and 12 were significantly lower in the fixed combination group compared to those of the β-blocker group (Table 3).[5] Higginbotham et al. also reported a significantly higher percentage of participants in the fixed-combination group achieving a mean diurnal IOP of $\leq$ 18 mmHg by the conclusion of the study, $p < 0.01$.[5]

Table 3. Mean diurnal IOP reported in Higginbotham et al.

	Mean diurnal IOP (SD), mmHg	
	Combination therapy	**β -blocker monotherapy**
Baseline	28.0 (2.2)	28.1 (2.3)
Week 6 [a]	17.9 (3.3)	20.9 (3.7)
Week 12 [b]	17.8 (3.5)	20.9 (3.5)

[a] Mean difference (95% CI): - 2.83 mmHg (-3.54 to -2.11 mmHg); $p < 0.001$
[b] Mean difference (95% CI): -3.02 mmHg (-3.79 to -2.24 mmHg); $p < 0.001$

Varna et al. reported a statistically significant ($p < 0.01$) lower mean diurnal IOP in patients treated with the fixed combination compared to those treated with β-blocker monotherapy, 19.4 mmHg and 22.4 mmHg, respectively. The differences from baseline to week 26 were -2.9 mmHg for the fixed combination group and -0.7 mmHg for the β-blocker group; $p < 0.01$.[6] The diurnal IOP fluctuation of participants in the fixed combination group was significantly lower in week 26 than was at baseline; $p = 0.002$; while there was a statistically insignificant increase in the diurnal IOP fluctuation of participants treated with β-blocker monotherapy; $p = 0.097$.[6] The between-treatment difference was statistically significant ($p < 0.01$) (Table 4).[6] The dichotomized data of the diurnal IOP fluctuation also demonstrated significantly fewer patients with "high" (> 6 mmHg) IOP fluctuation in the fixed combination group than in the monotherapy group; $p = 0.003$. There was a reduction in the percentage of participants with "high" IOP fluctuation in the fixed combination group (13.3% at baseline vs. 6.9% at week 26); whereas there was an insignificant increase in patients with "high" IOP fluctuation in the β-blocker monotherapy group (13.2% at baseline vs 14.9% at week 26; $p = 0.08$) (Table 5).[6] The number needed to treat based on the dichotomized diurnal IP fluctuation is 14.

Table 4. Mean diurnal IOP fluctuation at baseline and week 26 reported by Varna et al.

	Mean diurnal IOP fluctuation (SD), mmHg	
	Fixed combination	**β -blocker monotherapy**
Baseline	3.7 (2.5)	3.4 (2.3)
Week 26	3.0 (2.1)	3.7 (3.2)
Δ (baseline - wk 26) [a]	-0.68 (0.22) [b]	0.36 (0.22) [c]

[a] between-treatment p value: $p < 0.001$
[b] within-treatment p value: $p = 0.002$
[c] within-treatment p value: $p = 0.097$

Table 5. The number of participants with high (> 6 mmHg) and low (< 6 mmHg) mean diurnal IOP fluctuation as reported in Varna et al.

	Mean diurnal IOP fluctuation	
	Fixed combination	**β -blocker monotherapy**
Baseline [a]		
High (> 6 mmHg)	37 (13.3%)	28 (9.7%)
Low (< 6 mmHg)	241 (86.7%)	261 (90.3%)
Week 26 [b]		
High (> 6 mmHg)	19 (6.9%)	41 (14.4%)
Low (< 6 mmHg)	256 (93.1%)	243 (85.6%)

Number needed to treat: 14
[a] between-treatment p value: $p = 1.078$
[b] between-treatment p value: $p = 0.003$

The percentages of participants reporting an adverse event in Brandt et al. were 41% (221/533) for the fixed combination group and 24.7% (65/263) for the β-blocker group, $p < 0.001$. The percentage of participants in Higginbotham et al. reporting an adverse event were 29.5% (49/134) for the fixed combination group and 23.7% (31/131) for the β-blocker group, with total numbers of reported adverse events of 58 and 48, respectively. However, the statistical significance of this difference between the two treatment groups was not included in the data. The number needed to harm was 6 for the Brandt et al. study and 17 for the Higginbotham et al. study (Table 6).

Table 6. Treatment-related adverse events reported in Brandt et al. and Higginbotham et al.

	ERR	**CER**	**RR**	**RRI**	**ARI**	**NNH**
Brandt et al.	0.415	0.247	1.68	0.68	0.168	6
Higginbotham et al.	0.295	0.237	1.24	0.245	0.058	17

DISCUSSION

All three included studies demonstrated that fixed combination prostaglandin analog/β-blocker is safe and significantly more effective than β-blocker monotherapy in the prevention of disease progression in patients with open-angle glaucoma.[4,5,6] The two active ingredients of the fixed combination provided additive IOP reduction by affecting the aqueous level in two different mechanisms: decreased aqueous humor production by β-blocker and increased aqueous outflow by prostaglandin analog.[1, 2] There was a significantly higher number of participants maintaining a IOP of $\leq$ 18 mmHg, which is the visual field progression threshold defined by the Advanced Glaucoma Intervention Study.[5] Lowering IOP reduces optic nerve damage and therefore halts the progression of the disease to complete blindness. The Collaborative Initial Glaucoma Treatment Study had suggested that a decrease in IOP of 35% or more could prevent the progression of optic nerve damage over a 5-year period.[5]

Brandt el al. and Higginbotham et al. reported greater numbers of treatment-related adverse events in participants treated with fixed combination therapy compared to those treated with β-blocker monotherapy. Neither study reported serious treatment-related adverse event that resulted in discontinuation of the study. The most common adverse event was conjunctival hyperemia. Other reported adverse events were burning sensation in eye, eye pruritus and dryness, growth of eyelashes, foreign body sensation,…[4,5] Brandt et al. suggested that the lower incidence of conjunctival hyperemia in patients treated with β-blocker monotherapy may be class-related. The β_2-antagonistic activity of β-blockers decreases nitric oxide production, consequently leading to less hyperemia.[4] Additionally, the unopposed alpha$_1$-agonistic effects of endogenous catecholamines due to β-blockade may also contribute to decreased hyperemia in the

β-blocker monotherapy group.[4] Overall, the fixed combination of prostaglandin analog/β-blocker is well-tolerated and safe for the prevention disease progression of open-angle glaucoma.

All three studies included in this review are randomized controlled trials with an adequate sample size. However, one limitation of the study performed by Varna et al. is limited is that it was a posthoc analysis.[6] Additionally, although fixed-combinations of prostaglandin analog/β-blocker provide superior IOP reduction than β-blocker monotherapy, these formulations are not yet available in the United States. Ganfort (bimatoprost 0.03% and timolol maleate 0.5%) is only available in certain countries, while Xalacom (latanoprost 0.005% and timolol maleate 0.5%) and DuoTrav (travoprost 0.004% and timolol 0.5%) are only available in Canada.[7]

CONCLUSION

Overall, fixed combination prostaglandin analog/β-blocker can be recommended for additional IOP reduction to help prevent disease progression in patients with open-angle glaucoma requiring more than one topical treatment. The fixed combination therapy was found to be safe and more effective than β-blocker monotherapy. Additionally, it is also well-tolerated; and its convenient simple dosing schedule increases patient adherence, maximizing long-term IOP reduction and therefore preventing the progression of the disease. Future study is warranted to determine whether the fixed combination therapy is superior to multi-drug regimens of its individual active components in prevention of OAG disease progression.

REFERENCES

1. Horton JC. Disorders of the Eye. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9096666. Accessed December 10, 2011.

2. Riordan-Eva P. Disorders of the Eyes & Lids. In: McPhee SJ, Papadakis MA, Rabow MW, eds. *CURRENT Medical Diagnosis & Treatment 2012*. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=2002. Accessed December 10, 2011.

3. Goldberg LD. Disease management program for glaucoma – has the vision become a reality? *Dis Manage Health Outcomes*. 2007;15(4):199-205.

4. Brandt JD, Cantor LB, Katz LJ, et al. Bimatoprost/timolol fixed combination: a 3-month double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension. *J Glaucoma*. 2008;17(3):211-216.

5. Higginbotham EJ, Olander KW, Kim EE, et al. Fixed combination of latanoprost and timolol vs individual components for primary open-angle glaucoma or ocular hypertension: a randomized, double-masked study. *Arch Ophthalmol.* 2010;128(2):165-172.

6. Varma R, Hwang LJ, Grunden JW, Bean GW. Using diurnal intraocular pressure fluctuation to assess the efficacy of fixed-combination latanoprost/timolol versus latanoprost or timolol monotherapy. *Br J Ophthalmol*. 2010;94(1):80-84.

7. Lexi-comp Online. http://ezproxy.pcom.edu:2103/crlsql/servlet/crlonline. Accessed December 10, 2011.