Beta-blockers and Prostaglandin Analogues: A comparative Meta-analysis of Efficacy and Suffering-efficiency of Representative Agents

By: Matthew Robert

Word Count: 3,760

Candidate Number: 00862 031

Table of Contents

Abstract

This investigation aimed to determine which type of anti-glaucoma eye-drop, beta-blocker or prostaglandin analogue, is superior in terms of their intra-ocular pressure lowering efficacy and their efficiency with regards to the discomfort of patients. Data from four clinical trials evaluating the safety and efficacy of the drugs over periods of at least 12 weeks (in most cases trials lasted more than three months) was used. Baseline IOP values in patient populations were taken from each study, as well as mean patient IOP values at either 12 or 13 weeks for each eye-drop. Predicted IOP values were calculated for studies which had not specified mean patient IOP reduction at 13 weeks. From IOP values at 13 weeks, predicted or otherwise, a mean percentage IOP reduction was calculated for each eye-drop. The mean percentage IOP reductions were then averaged for the two drug categories. A table was constructed to show all adverse reactions experienced by patients relevant to their prescribed eye-drop, and these were generalised to the two drug types in a graph of common adverse-events reported. The results of the meta-analysis were that; the prostaglandin analogues produced a 4.9 mmHg superior average mean IOP reduction value than the beta-blockers; only 3% of patients using prostaglandin analogues suffered from burning/stinging of the eyes compared to 70% of patients using beta-blockers, though 1% more prostaglandin analogue using patients suffered hyperaemia of the lid and/or conjunctiva than beta-blocker using patients. Considering the generally more severe possible side-effects of beta-blockers and the much less frequent occurrence of burning/stinging of the eyes in patients using prostaglandin analogues, as well as the superior performance of prostaglandin analogues in terms of mean IOP reduction at 13 weeks, I concluded that prostaglandin analogues are generally superior to beta-blockers in terms of IOP lowering efficacy and patient comfort.

Introduction

Often called 'the silent thief', the disease glaucoma has been identified by ophthalmologic studies as being among the world's leading causes of blindness, having been identified second only to cataracts by the World Health Organization in 2007 ("Causes of blindness and visual impairment"). Glaucoma is not itself one disease, but rather a group of chronic eye diseases which cause irreversible deterioration of the optic nerve. While treatment of the various glaucomas is somewhat dependent on the specific diagnosis, all treatments focus on the lowering of the pressure inside the eye's globe, called the intra-ocular pressure (IOP, measured in millimetres of mercury - mmHg). This is because most glaucomatous patients express a heightened intra ocular pressure and, while we cannot directly cure glaucoma itself, lowering the intra-ocular pressure in glaucomatous eyes is known to reduce or at times halt the process of deterioration of the optic nerve.

Adult glaucoma has two sub-categories, distinguished by the causes of the heightened IOP in the differing types. These sub-categories are: open angle glaucoma, characterized by the clogging of drainage canals in the eye, and closed angle glaucoma, characterized by the blocking of the eye's drainage canals by the iris root. Another condition, called ocular hypertension (OHT), is diagnosed when a patient's IOP is measured to be above the 'normal' threshold on two or more occasions despite showing no signs of glaucoma. People diagnosed with OHT are usually monitored more closely than the general population for the onset of glaucoma. This investigation focuses solely on the treatment of open angle glaucoma and ocular hypertension.

As had been said, treatment of glaucomatous eyes revolves around the lowering of the intra-ocular pressure of the eyes, and this is true even in cases of glaucoma in which the eyes have a 'normal' IOP. The methods by which intra-ocular pressure is lowered are several. Upon diagnosis of glaucoma, an ophthalmologist will determine whether medical therapy, laser therapy or surgery is the best form of treatment for the patient. Surgical treatment is usually resorted to only when IOP and the rate of deterioration of the optic nerve persist despite previous therapies, while laser therapy is not commonly used as a method of treating open angle glaucoma. Medical therapy will usually be the form of treatment initially applied to glaucoma patients, and many will rely on medical therapy exclusively throughout the term of their treatment.

Anti-glaucoma medical therapy focuses on the use of eye drops, of which there is moderate variety. These eye-drops can be separated according to their affect on the flow of aqueous humour (the water-like fluid in the eye's posterior and anterior chambers: see diagram) through the eye. Some eye-drops reduce the IOP by decreasing the production/inflow of

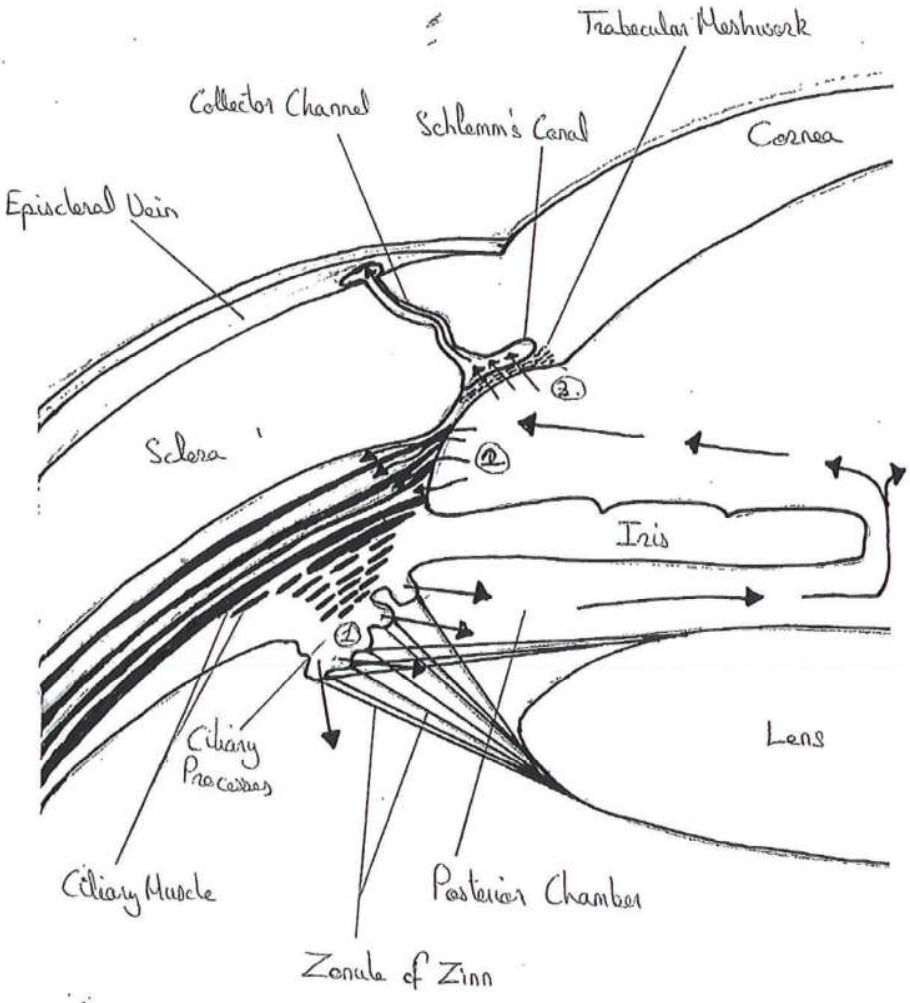
aqueous humour from the eye's cilliary body, while others increase the outflow of aqueous humour through either the trabecular meshwork pathway (into Schlemm's canal) or the uveoscleral pathway (into the sclera and the choroid).

While I was researching these eye-drops, I became interested in determining any differences between the different functional groups (outflow, inflow) in terms of their ability to lower and stabilize IOP. While there was an abundance of research comparing individual chemical eye-drops, and even comparing two different eye-drops from the same functional group which work differently, I noticed a lack of research comparing the efficacy of drugs which decrease aqueous production to drugs which facilitate aqueous drainage. Thus, I decided to conduct a meta-analysis over several studies comparing individual eye-drops in such a way as to have sufficient data to compare one type of drug which decreases aqueous inflow to one type of drug which increases aqueous outflow. I would then balance this data against the various side effects of the medication types and specific medications to reach a conclusion as to which type of topical eye-drops is the more efficient and advisable medication.

With regards to the type and specific drugs investigated, I chose to compare the beta-blockers levobunlol, metipranolol and timolol to the prostaglandin analogues latanoprost, bimatoprost and travoprost. Beta-blockers are substances which, when applied to the eyes via eye-drops, reduce the production of aqueous by the eye's cilliary body through the blocking of the eye's beta adrenergic receptors which are a key component to the production of the aqueous fluid. Conversely, prostaglandins are naturally occurring hormones with a wide range of functions. When used in ophthalmic solutions, prostaglandin analogues facilitate the outflow of the aqueous humour through the uveoscleral pathway, seemingly by increasing the absorption of aqueous by uveal tissue.

The specific drugs I chose to represent each category were chosen based on the availability of data. All data pertaining to levobunlol and timolol was obtained from the same clinical trial (Ober, Scharrer, David, Biedner, and Novack 593-599). Metripranolol data was obtained alone from one trial (Krieglstein, Novack, Voepel, Schwarzbach, and Lange 250-253). Likewise, bimatoprost and travoprost data was obtained from the same trial (Cantor, Catoira, Hoop, Morgan, and WuDunn 1370-1373) while latanoprost data was obtained alone from one trial (Baudouin, Bron, Denise, Nordmann, and Renard).

Diagram to Show the Flow of Aqueous Humour Through the Posterior and Anterior Chambers In One Half of the Eye



Key:

→ : Direction of Flow of Aqueous Humour.

① : Site of production of aqueous humour (the ciliary processes).

② : Uveoscleral outflow

③ : Trabecular outflow

Methodology

The methodology has been split into three sections. The first is a general explanation of tonometry, the process by which ophthalmologists and opticians measure IOP. The second deals with the common procedures of the four clinical trials (for specific methodologies see references). The third section shows my method of predicting unmeasured IOP values and the rationale behind my methodology.

1. Tonometry

Tonometry is the name given to the indirect measurement of IOP by deforming the eye's surface through an applied force and calculating the intra-ocular pressure from measures of the eye's resistance to the deforming force (Alguire). Tonometers are classified according to their method of deforming they eye, either by applanation (flattening) or indentation. As all the clinical trials from which this analysis' data is sourced either specified use of an air pulse tonometer or Goldmann tonometers, both of which work via flattening, or did not specify the method of tonometry at all, I have only outlined applanation tonometry.

Of all applanation tonometers currently in use, the Goldmann tonometer is the 'gold standard'- the instrument considered most accurate against which all other tonometers are composed. The Goldmann tonometer is designed to be mounted on a slit lamp. Part of the tonometer- a plastic biprism- is placed in contact with the patient's cornea producing two semi-circular rings. The tonometer's operator sees these rings through the plastic bi-prism and can tell when a pre-determined area of the cornea has been flattened as the two semi-circular rings will converge at that time, indicating the endpoint has been reached. It is at this point that the IOP in the eye currently being examined is read off the machine's scale.

While the study evaluating the efficacy of levobunlol specifies an 'air-pulse tonometer' this is most probably a specified reference to the increasingly popular noncontact tonometer, known for ease of use and accuracy. The noncontact tonometer uses a puff of air to cause corneal deformity in place of the direct application of force applied by Goldmann tonometers. The time taken to deform the cornea is identified through the difference in the cornea's ability to reflect a beam of light to a reference point. It is this time value which is the dependant variable related to intra-ocular pressure. This is done through comparison of previous measurements taken by a Goldman tonometer- hence the Goldmann tonometer's status as the 'golden standard'.

2. Trial Methodologies

A. Patient Eligibility

Table 1: Common Inclusion Criteria by which Prospective Participant Suitability was Assessed

Inclusion Criteria	Clinical Studies which Specify Relevant Criteria, Identified by The Drugs for which Their Data was Used.			
	Timolol, Levobunolol	Metipranolol	Latanoprost	Bimatroprost, Travoprost
Minimum IOP (mmHg)	23	22	20	21
Maximum IOP (mmHg)	-	-		34
Minimum Age Requirement (years)	-	-+	18	18
Necessary Diagnosis	COAG or OHT	COAG or Secondary Glaucoma or OHT	OHT or OAG (including: POAG, Pseudoexfoliation Glaucoma or Pigmentary Glaucoma)	COAG or OHT

Table2: Common Exclusion Criteria

Common Exclusion Criteria	Timolol, Levobunolol	Metipranolol	Latanoprost	Bimatoprost, Travoprost
Pregnancy, Expected Pregnancy or Lactation, Inadequate Birth Control Methods	✓		✓	✓

Known Contradictions to systemic or Topical use of B-blocking Agents/Known Cardiac or Pulmonary Conditions which would Contradict the Use of Beta Blockers	✓	✓	✓	
Use of Adregenic-augmenting Psychotropic Drugs	✓			
Use of Topical or Systemic Corticosteroids	✓			
Sever Diabetes Resulting in Change of Insulin Dosage	✓			
Aphakia, Chronic Ocular Inflammation, or Any Corneal Abnormalities Preventing Reliable Applanation Tonometry	✓		✓	
Severe COAG Uncontrolled by Concomitant Administration of Two or More Anti-glaucoma Drugs	✓			
Inability to Tolerate Washout of Pre-study Anti-glaucoma Medications	✓			
Contact Lens Wear During the Study Duration				
Adverse Reaction to the Study Medication		✓		✓
Inadequate Control of IOP Defined as Unacceptably High Intraocular Pressure (22mmHg+) in Each Eye on Two Consecutive Morning Visits 24-28 Hours Apart		✓		
Uncontrolled Systemic Disorder/Disease			✓	✓
Functionally Marked Visual Field Loss				✓
Ocular Surgery Within The Last Three Months				✓
Concomitant Usage of Ocular Drugs (Except Intermittent Use Of Artificial Tears)				✓
Planned Change in Ongoing Systemic Treatment That Might Affect IOP				✓
Participation In Another Clinical Trial In The Last Thirty Days.				✓

It is important to note that the lack of specification of certain inclusion/exclusion criteria does not necessarily mean that it was not part of the criteria. For instance, while not all the journal articles specified the minimum age requirement of 18 years, it is reasonable to presume that this was common inclusion/exclusion criteria to all the trials, and indeed in none of the patient demographic tables does the range of age of patients extend to below 18 years.

B. Trial Procedure

The common procedures have been outlined in chronological order as far as the variance in procedure between the studies would allow. While I have specified some variations where doing so did not require excessive deliberation, a more accurate understanding of the methodologies may be obtained via consultation of the original journal articles.

Either before or at the baseline IOP measurement, patient eligibility was assessed according to the above criteria. Once eligibility was confirmed, patient demographics (age, diagnosis, sex, race and eye colour) were recorded. Differing washout periods were required of patients depending on whatever topical medication they had previously been using, as well as the trial in question. Before the first application of the topical medication, baseline intra-ocular pressure measurements were taken and recorded, either via Goldman applanation tonometry or air pulse tonometry. Following the baseline measure, the first of all following measurements of IOP (in those studies which measured IOP multiple times in one day; otherwise the only IOP measurement) would be taken before the designated morning application of medication.

As anti-glaucoma beta-blockers are applied twice daily, participants prescribed with beta-blockers were asked to apply their eye-drops in the morning and evenings (9 am and 9pm for timolol and latanoprost, 7-8:30am and 9:30-11pm for metipranolol). Conversely, prostaglandin analogue eye-drops are applied once daily, and participants were asked to apply their eye-drops in the evenings (between 19:00 and 21:00 for bimatoprost and travoprost, unspecified as ‘in the evening’ for latanoprost). At each following visit, IOP was measured, presumably using the same type of tonometer (specified in the timolol/latanoprost and levobunlol efficacy trials).

Other measurements were also taken at each follow-up visit than the intra-ocular pressure. Among these were the measures of corneal sensitivity and, in the beta-blocker trials, blood pressure and heart rate. Shirmen’s test, which measures tear production, was also carried out in the levobunlol/timolol efficacy trial. A complete ocular examination was conducted in each follow up visit in the bimatoprost/travoprost efficacy trial, while biomicroscopy, opthalmoscopy and an eyelid examination were performed at each visit in the latanoprost efficacy trial. In all

the eye-drop efficacy trials patient complaints of adverse events were recorded, as well as the investigator's opinion as to whether or not the event was related to the study drug.

3. Method of Results Calculation

Table 3: Mean IOP Reduction in Patients Using Beta-blockers Used to Predict Mean IOP Reduction at Week 13

	Mean Intraocular Pressure Changes From Baseline Value (mmHg)(Standard Deviation)		
Point in Study Period (weeks)	0.5% Levobunolol (IOP, SD)	0.6% Metipranolol (IOP, SD)	0.5% Timolol (IOP, SD)
0 (baseline, zero change)	27.9 ±5.5	26.0 ±3.6	26.4 ±2.8
6	-7.2 ±3.0	NV*	-6.7 ±3.0
8	-6.9 ±3.6	-7.1 ±2.9	-6.3 ±2.9
10	-6.9 ±3.8	NV	-6.5 ±3.1
12	-6.9 ±3.4	-6.9 ±3.8	-6.4 ±3.0

*NV= no value given

Rationale

It would have been possible to average the mean IOP reduction values at weeks 6, 8, 10 and 12 and use this as a value for week 13. However, I instead decided to calculate the average change in IOP every two weeks from week six, then halved this value and added it to the mean IOP reduction value at week 12, producing a predicted mean change in IOP for week 13 (see table 4). I decided that this would be the more suitable method because it would fit more accurately on a plot of the mean change in IOP in each trial. For example, if one was to plot the last four mean IOP changes in levobunlol patients, they would see a downward slope which has reached a plateau. While a mean of the last four mean IOP reduction values for levobunlol would produce a predicted 5^{th} value which would cause the graph to curve upwards, this is not what was actually exhibited. Thus I averaged the change in the mean IOP reduction from week to week and added it to the week 12 IOP reduction value, producing a value which would plot a downward curve. From the raw data in the levobunlol trial it can be seen that the efficacy of 0.5% levobunlol eye drops did, in fact, gradually decrease over time, and as such my chosen method did indeed produce a more accurate and probable predicted value for the mean IOP reduction at week 13.

The predicted value for the mean IOP reduction in patients using metipranolol was calculated by adding the difference between mean IOP reduction values at weeks 8 and 12 (+0.2) to the mean IOP reduction value at week 12.

With regards to the analysis of adverse events experienced by patients, analysis was made difficult by the fact that the different drug types have many side effects unique to their own type. As such, a table of all reported adverse events was constructed, but a graph was made to directly compare the incidences of occurrence of side effects common to both drug types. A table of drug specific side-effects is also available in Appendix 2.

Table 4: Predicted Mean IOP Change at 13 weeks for Patients Using Beta-blocker Eye-drops

	Changes in Mean Intraocular Pressure Changes From Baseline Value (mmHg)(Standard Deviation)		
Interval In Study Period (week A to week B)	0.5% Levobunolol	0.6% Metipranolol	0.5% Timolol
6-8	+0.3	NV	+0.4
10-12	+0.0	NV	+0.2
10-12	+0.0	NV	+0.1
Mean Change in Change in IOP from Baseline (mmHg) to 1 significant figure	+0.1	+0.2	+0.2
Predicted Mean Change In IOP at Week 13 (mmHg)	-6.8	-6.9*	-6.2

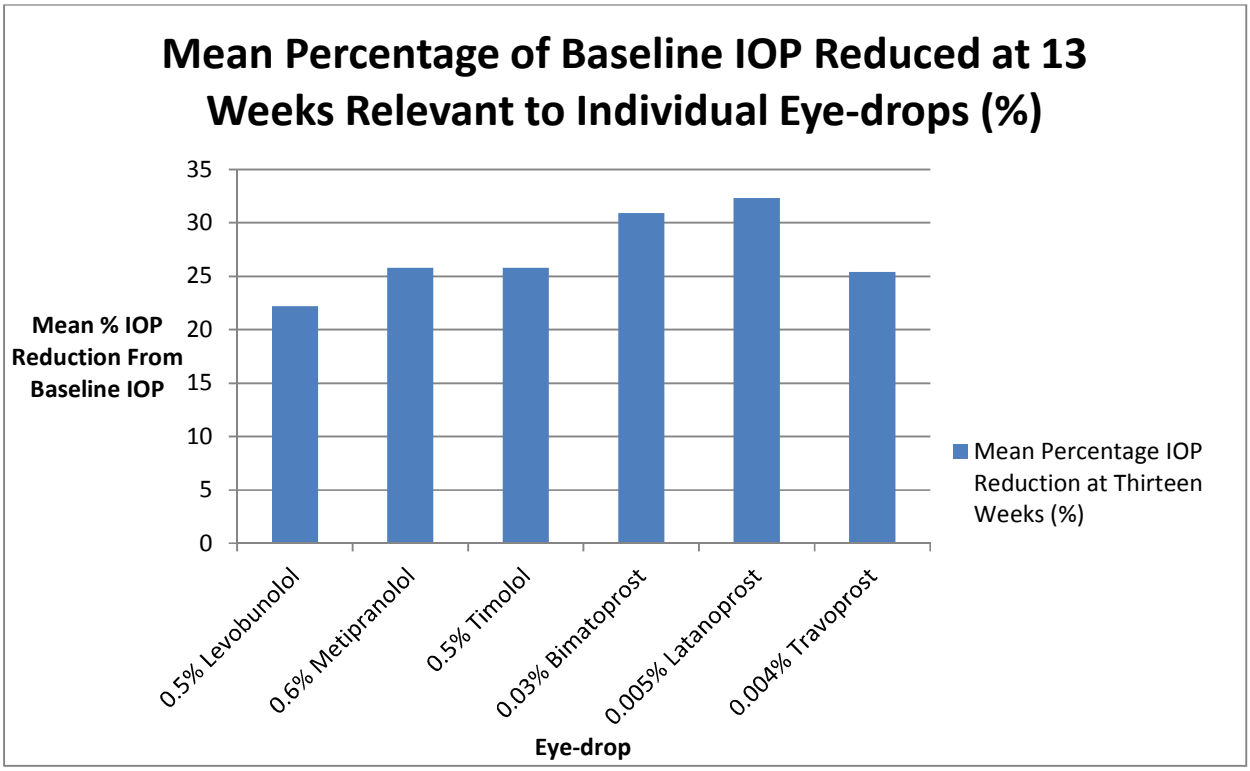
Results

Mean Percentage IOP Reduction at 13 Weeks and Average Mean Percentage IOP Reduction at 13 Weeks in Patients Using Different Eye-drop Types

	Mean Intraocular Pressure Changes From Baseline Value (mmHg)(Standard Deviation)					
	Beta-Blockers			Prostaglandin Analogues		
Study Period (weeks)	Levobunolol 0.5%	Metipranolol 0.6%	Timolol 0.5%	Bimatoprost 0.03%	Latanoprost 0.005%	Travoprost 0.004%
0 (Baseline)	27.9	26.0	26.4	24.6	24.45	24.4
13	-6.2	-6.7	-6.8	-7.6	-7.9	-6.2
Mean Percentage IOP Reduction (%)*	**22.2**	25.8	25.8	30.9	32.3	**25.4**
Average Mean Percentage IOP Reduction Relevant to Drug Type (%)	24.6			29.5		

* Percentages to three significant figures

Bold: Values which did not fit the trend are in bold. However, because the trials were done over 12-13 weeks using many patients, these are not necessarily 'anomalous' results and as such have been included in averages.


Mean Percentage of Baseline IOP Reduced at 13 Weeks Relevant to Individual Eye-drops (%)
Mean % IOP Reduction From Baseline IOP
35
30
25
20
15
10
5
0
0.5% Levobunolol
0.6% Metipranolol
0.5% Timolol
0.03% Bimatoprost
0.005% Latanoprost
0.004% Travoprost
Eye-drop
Mean Percentage IOP Reduction at Thirteen Weeks (%)

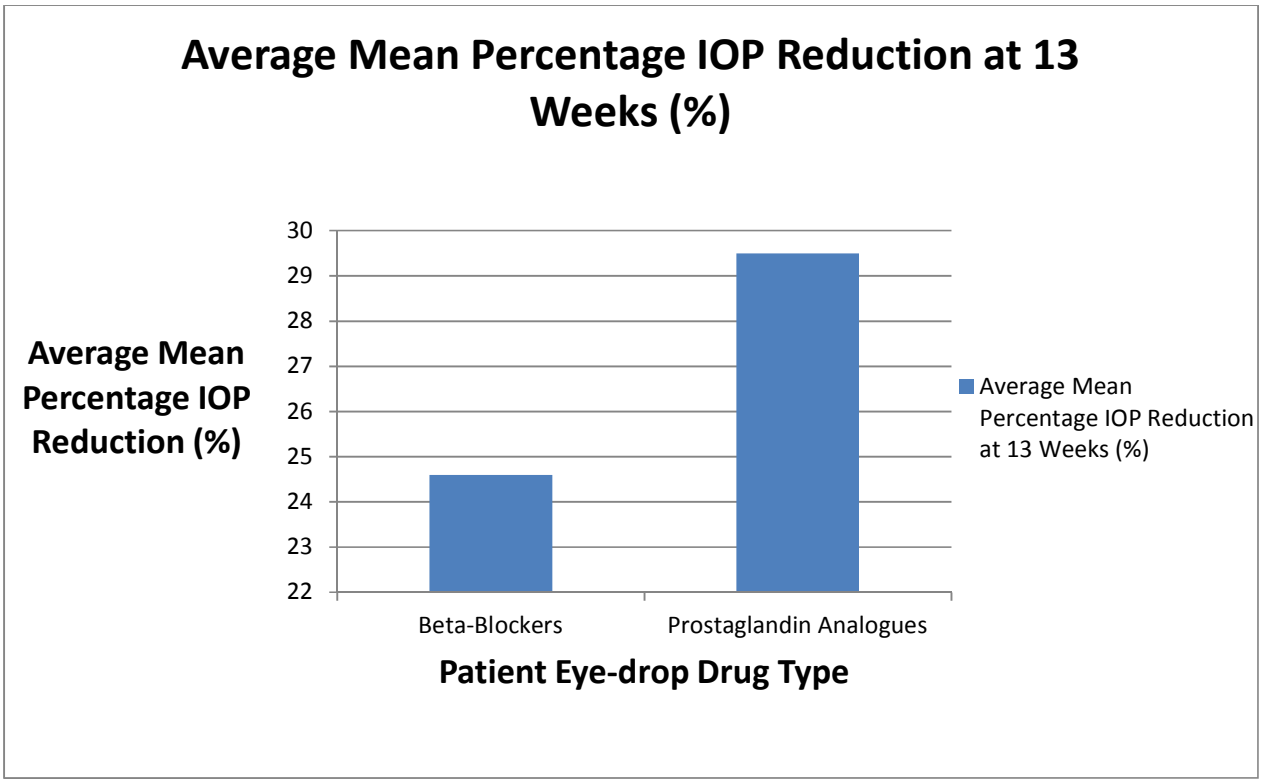
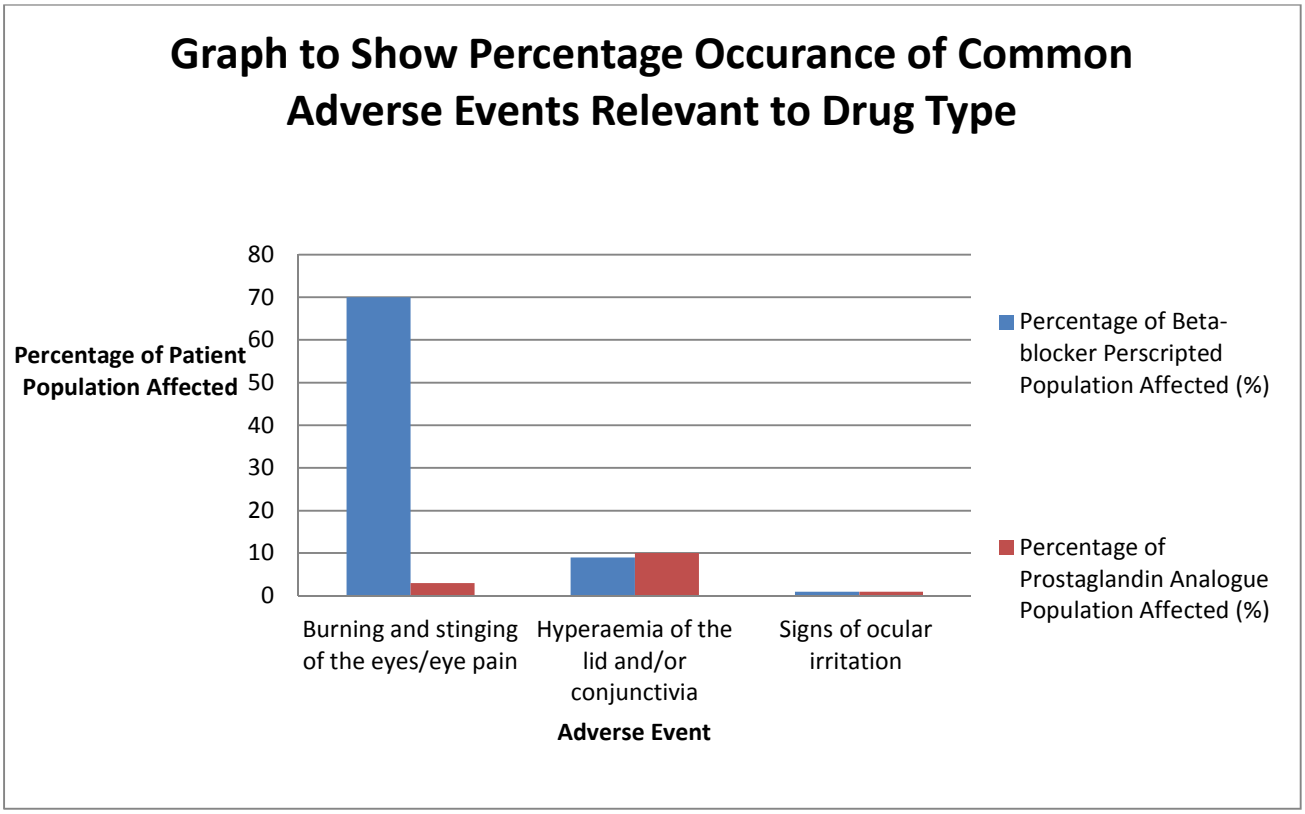

Average Mean Percentage IOP Reduction at 13 Weeks (%)
Average Mean Percentage IOP Reduction (%)
30
29
28
27
26
25
24
23
22
Beta-Blockers
Prostaglandin Analogues
Patient Eye-drop Drug Type
Average Mean Percentage IOP Reduction at 13 Weeks (%)

Table to show frequency of adverse patient reactions to the various eye-drops

	Frequency Of Trial Subject Report of Adverse Event For Different Prescriptions (number of patients, percentage of the sample population)					
Adverse Event	Metipranolol N %	Levobunolol N %	Timolol N %	Latanoprost N %	Bimatoprost N %	Travoprost N %
Burning and stinging of the eyes/eye pain	8-10* 38-56	1 3	-	19 3	-	-
Hyperaemia of the lid and/or conjunctivia	6 26	-	-	48 8	16 21	12 15
Signs of ocular irritation (blepharitis, conjunctival erythema)	-	1 3		4 1	1 1	2 2
Headaches	-	1 3	-	-	-	-
Heartburn	-	1 3	-	-	-	-
Diarrhoea		1 3				
Eyelid/ocular pruritis	-	-	-	4 1*	2* 2	6 7
Eye abnormality NOS	-	-	-	4 1*	-	-
Keratitis	-	-	-	4 1*	-	-
Eyelid edema	-	-	-	3 1*	-	-
Photophobia	-	-	-	1 1*	1 1	-
Vision Abnormal NOS*	-	-	-	1 1*	-	-
Xerophthalmia	-	-	-	1 1*	-	-

*(8-10 at each follow up visit). *NOS: not otherwise specified. *-: 0 patients affected *all % values between 1 and 0 were rounded to 1 *patient number values to the nearest whole number



Discussion & Conclusion

From the graph showing the average mean percentage IOP reduction values at 13 weeks it can be seen that the prostaglandin analogues generally provided a greater percentage IOP reduction than the beta-blockers, achieving an average mean IOP reduction 4.9 mmHg superior to that produce by the beta-blockers. Of the prostaglandin analogues, the greatest mean percentage IOP reduction in patients from their mean baseline IOP values was 32.3mmHg, provided by 0.005% latanoprost. Conversely, the smallest percentage IOP reduction from the mean baseline IOP of patients was 22.2mmHg, provided by the beta-blocking agent levobunolol. Both metipranolol and timolol provided a mean IOP percentage reduction from mean baseline value of 25.8mmHg, 0.4mmHg more than that provided by travoprost, the least effective of the prostaglandin analogues in terms of IOP reducing efficacy.

As two of the three prostaglandin-analogues provided significantly higher mean percentage IOP reduction values relative to mean baseline values, it can be said that the prostaglandin-analogues were generally more effective in terms of lowered intra-ocular pressure than the beta-blockers. It is important to note that this is a general assertion; the large standard deviation values recorded in the methodology's data tables for patients using beta-blockers, as well as the large standard deviations noted in the IOPs of patients using prostaglandin analogues (see appendix) indicate the significance of individual response to various medications. Such pronounced variations in the ability of generally successful treatments to control IOP mean that any deduction form the data can only be legitimate as a generalization- some patient's IOP will not be controlled by medications shown to be very successful in controlling the IOP of other people.

A similar difficulty presents itself when attempting to assess one group as being more 'suffering-efficient' than the other because of the differing side-effects of the two drug types, as well as the differing individual patient reactions. From the table of recorded treatment-related adverse events experienced by patients, it can be seen that the greatest range of side-effects was exhibited by patients using latanoprost eye-drops; the smallest range was seen in patients using metipranolol eye-drops. The most common side-effects experienced by all patients using prostaglandin analogue eye-drops were hyperaemia, either ocular or of the lid or conjunctival. The least frequently occurring side-effects were headaches, diarrhoea, unspecified visual abnormality and xeropthalmia. As can be seen from the graph showing the percentage of patients using each drug type affected by common side-effects, only 1% of patients using either drug type showed signs of ocular irritation, and a 1% greater percentage of participants using prostaglandin analogues suffered hyperaemia of the lid and or hyperaemia of the conjunctiva. However, a significantly greater percentage (67%) of the participants using beta-blockers suffered from burning/stinging of the eyes than the percentage of prostaglandin analogue using participants who suffered those side-effects.

Heartburn and diarrhoea are symptoms specific to beta-blockers, and as such were only experienced by a patient using the beta-blocker levobunlol. Likewise, eyelid and ocular pruritis, side-effects associated with prostaglandin analogues, were expressed only in 1% of latanoprost patients, 2% of bimatoprost patients and 7% of travoprost patients. As well as considering the possible side effects of various eye-drops, it is also important for ophthalmologists to consider the severity of these effects. On the whole, beta-blocker specific side effects carry more risks to a greater range of people than prostaglandin-specific side effects. This is because beta-blockers may cause constriction of blood vessels and airways, as well as dull the signs of low blood sugar (Appendix 2). Evidently, this makes beta-blockers an unsafe choice for patients suffering from pulmonary or breathing disorders, as well as diabetes. While side-effects such as pruritis may occur more frequently than the systemic side-effects of beta-blockers, a risk of itching of the

eye is certainly preferable to a risk of diarrhea, breathing difficulty and pulmonary abnormalities, especially when prescribing medication for patients with disorders or diseases which would be aggravated by these effects.

While the large variations in individual response to all eye-drops and the string of side effects associated with both groups may appear to make comparison of one group to the other redundant, this is not the case. So long as there is no negative compromise to the efficacy of treatment of elevated IOP in patients diagnosed with ocular-hypertension or open-angle glaucoma, it is always preferable to prescribe as few different medications as possible. This is because the use of plural drugs (e.g. concomitant use of bimatoprost and travoprost eye-drops) results in an increased range and risk of side-effects. Not only does this compromise the patient's safety and comfort, but it also decreases the likelihood of the patient complying with their treatment program. Furthermore, proof of general superior efficacy in terms of lowering IOP helps ophthalmologists to prescribe new eye-drops when previous treatment has failed to control a patient's IOP. As such, I have judged prostaglandin analogues to be the eye-drops which are preferable in terms of patient discomfort, as most side effects related to prostaglandin analogues are either minor or cosmetic and thus do not place patients with pulmonary disorders or breathing disorders at risk.

In conclusion, the prostaglandin analogues generally provided greater mean percentage of baseline IOP reduction values at week thirteen than the beta-blockers. This, combined with the advantage of prostaglandin analogues over beta-blockers in that prostaglandin analogues have largely cosmetic side-effects rather than systemic side-effects, has led me to conclude that prostaglandin analogues are the more discomfort-efficient and effective type of topical anti-glaucoma medication.

Evaluation

As is the nature of a meta-analysis, my investigation is limited in both reliability and validity in various ways, all of which are subject to the discrepancies between the methodologies and patient demographics of the four different investigations from which my data is sourced.

Regarding the reliability of the results, differences in sample sizes have meant that the results from some studies were more reliable than others. The number of patients who remained in the studies at weeks 12/13 were 21(levobunolol), 25(timolol), 23(metipranolol), 76(bimatoprost), 81(travoprost) and 582(latanoprost). The very large differences between the individual population sizes, as well as between the beta-blocker and prostaglandin analogue studies in general, means that the values for the mean percentage reduction in IOP from the mean baseline values calculated for the prostaglandin analogues are far more reliable values than those calculated/predicted for the beta-blockers.

In terms of the results themselves, the fact that all the beta-blocker evaluating investigations measured patient IOPs at week 12 and the prostaglandin analogues measured patient IOPs at three months (13 weeks) meant that mean reduction in patient IOP relative to baseline values had to be predicted using the week 12 values and average changes in IOP reduction every two weeks. This compromises the validity of the results because predicted values follow previous trends, and thus cannot accurately represent possible oscillations in the IOP of the patients across weeks.

In terms of uncertainty values/standard deviations, I could not produce predicted standard deviation values for week thirteen, nor was it possible to produce standard deviations values for the bimatoprost and travoprost data due to the chosen method of data analysis in the trial evaluating their efficacies. Returning to the previous point, the standard deviations in the beta-blocker data sets are more vulnerable to distortion by outliers than those in the prostaglandin analogue data sets due to the beta-blocker efficacy trials having smaller patient samples.

Returning to the limitations caused by variations in patient demographics, the different racial majorities in the different studies as well as differing inclusion/exclusion criteria with regards to required diagnosis (some studies accepted a secondary glaucoma diagnosis, others did not) reduces the reliability of the results. This is because we cannot be sure that different races and eyes with different specific causes of blockage of aqueous outflow respond equally to the drugs tested.

Basic differences in methodologies may also have reduced the validity and accuracy of the results. The use of unspecified tonometers in all but the levobunolol trials is significant in that some measurements of IOP may have been less accurate than others due to differing apparatus. The results levobunolol trial, having specified constant use of either a Goldmann tonometer or an air-pulse tonometer based on whichever was used to measure baseline IOP, may also be subject to reduced accuracy due to the comparatively lower accuracy of non-contact tonometers to the Goldmann tonometer. Having said this, any inaccuracies in tonometry would have had little overall effect on the validity of the results as inaccuracies would be small and minimized through the taking of averages.

Regarding possible improvements to the methodologies as well as the meta-analysis overall, a meta-analysis investigating the same subject but using studies with specified mean IOP reduction values at the same point in the studies following the baseline measurements would eliminate the need for predicted values and thus prevent such a loss to the validity and reliability of results. Likewise, if all the studies included in the meta-analysis were to provide mean IOP reduction values *after* determined time spans instead of *at* determined time spans, much more useful and reliable comparisons could be made. The prostaglandin analogue trials sourced in this analysis provided mean IOP reduction values at 3 weeks instead of after 3 weeks, therefore the data used was subject to outliers/oscillations in the IOP lowering efficacy of the eye-drops tested. Furthermore, the unanimous use of Goldmann tonometers would also have ensured as near optimum accuracy as possible data-wise. Finally, while all of these are valid improvements to a meta-analysis, any single long-term investigation into the efficacy of various prostaglandin analogues and beta-blockers would mean that the methodology of measuring IOP and selecting participants, as well as the demographics of the patients would all be constant by default, preventing any loss of validity or reliability of results via methodological discrepancies.

References:

Alguire, Patrick. "Tonometry." *Clinical Methods* (1990): n. pag. Web. 21 Nov 2010. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=cmð=A3603>.

Alm, Albert, Ian Grierson, and Bruce Shields. "Side Effects Associated with Prostaglandin Analog Therapy." *Survey of Ophthalmology* 53.6 (2008): S93-S105. Web. 21 Nov 2010. <http://www.surveyophthalmol.com/article/S0039-6257%2808%2900129-X/abstract>.

Baudouin, Christophe, Alain Bron, Philippe Denise, Jean-Philippe Nordmann, and Jean Paul Renard. "First-line latanoprost therapy in ocular hypertension or open-angle glaucoma patients: a 3-month efficacy analysis stratified by initial intraocular pressure." *British Journal of Ophthalmology,* 2010. n. pag. *British Journal of Ophthalmology,*. Web. 21 Nov 2010. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2841111/>.

"Beta-blockers." *Bupa*. Bupa, 09/2009. Web. 21 Nov 2010. <http://hcd2.bupa.co.uk/fact_sheets/html/beta_blockers.html#6>.

"Beta-Blockers." *Health Patient UK*. EMIS, 15/06/2009. Web. 21 Nov 2010. <http://www.patient.co.uk/health/Beta-Blockers.htm>.

Cantor, L B, Y Catoira, J Hoop, L Morgan, and D WuDunn. "Intraocular pressure-lowering efficacy of bimatoprost 0.03% and travoprost 0.004% in patients with glaucoma or ocular hypertension." *British Journal of Ophthalmology,* 2006. 1370-1373. *British Journal of Ophthalmology,*. Web. 21 Nov 2010. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1857505/>.

"Edema." *Medical Dictionary Online*. N.p., n.d. Web. 21 Nov 2010. <http://www.online-medical-dictionary.org/Edema.asp?q=Edema>.

"Glossary of Medical Terms- Ophthalmology." *East Valley Ophthalmology*. East Valley Ophthalmology, n.d. Web. 21 Nov 2010. <http://doctor-hill.com/patients/glossary.htm>.

"Hyperemia." *Medical Dictionary Online*. N.p., n.d. Web. 21 Nov 2010. <http://www.online-medical-dictionary.org/omd.asp?q=Hyperemia>.

"Keratitis." *Medical Dictionary Online*. N.p., n.d. Web. 21 Nov 2010. <http://www.online-medical-dictionary.org/omd.asp?q=keratitis>.

Krieglstein, G K, G D Novack, E Voepel, G Schwarzbach, and U Lange. "Levobunolol and metipranolol: comparative ocular hypotensive efficacy, safety, and comfort." *British Journal of Ophthalmology,* 1987. 250-253. *British Journal of Ophthalmology,*. Web. 21 Nov 2010. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1041137/pdf/brjopthal00614-0007.pdf>.

Ober, Manuel, Armin Scharrer, Robert David, Ben-Zion Biedner, and Gary D Novack. "Long-term ocular hypotensive effect of levobunolol: results of a one-year study." *British Journal of Ophthalmology* 593-599. *British Journal of Ophthalmology*. Web. 21 Nov 2010. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1040686/pdf/brjopthal00140-0037.pdf>.

"Pruritis." *Medical Dictionary Online*. N.p., n.d. Web. 21 Nov 2010. <http://www.online-medical-dictionary.org/omd.asp?q=pruritis>.

United Nations. *Causes of blindness and visual impairment*. World Health Organization, 2002. Web. 21 Nov 2010. < http://www.who.int/blindness/causes/en/>.

"Xerophthalmia." *Medical Dictionary Online*. N.p., n.d. Web. 21 Nov 2010. <http://www.online-medical-dictionary.org/omd.asp?q=Xerophthalmia>.

Bibliography

Cassel, Gary H, Micheal D Billig, and Harry G Randall. *The Eye Book: A complete Guide to Eye Disorders*. Baltimore: The Johns Hopkins University Press, 1998. 164-169, 179-183. Print.

Flammer, Joseph. *Glaucoma*. 3rd ed. Basel: Hogrefe&Huber Publishers, 2002. 31-35, 45-53, 151-161. Print.

Appendix 1

Glossary

Aphakia: 'Absence of the lens of the eye.'^

Blepharitis: 'Inflammation of the eyelids'^

Conjunctiva: 'Mucous membrane lining the inner surface of the eyelids and covering the front part of the sclera (white part of eye), responsible for keeping the eye moist.'^

Conjunctival: Pertaining to the conjunctiva

Conjuctival hyperaemia: hyperaemia of the conjunctiva

Conjunctivitis: 'Inflammation or irritation of the conjunctiva. Symptoms can be present in just one eye, or it can affect both eyes and include redness of the eyes or the edges of the eyelids, swelling of the eyelids or itching.'^

Edema: 'Excessive amounts of watery fluid accumulated in the intercellular space.' *

Erythema: 'Redness of the skin produced by congestion of the capillaries.' *

Eyelid edema: Edema of the eyes.

Hyperaemia/hyperemia: 'The presence of an increased amount of blood in a art or organ'*

Keratitis: 'Inflammation of the cornea.'*

Photophobia: 'Sensitivity to light.'^

Pruritis: 'An intense itching sensation that produces the urge to rub or scratch the skin to obtain relief'*

Xerophthalmia: 'Dryness of the eye surfaces caused by deficiency of tears or conjunctival secretions.'*

Source Key

''^: "East Valley Ophthalmology"

''*: "Medical Dictionary Online"

Appendix 2

Table of Side Effects Unique to Prostaglandin Analogues and Beta-blockers Separately

Drug Type	Possible Side Effects of Drug Use
Prostaglandin Analogue	• Darkening of iris pigmentation • Increased length and number of eye-lashed • Conjunctival hyperemia • Periocular skin pigmentation
Beta-blocker	• Slowing heart rate • Narrowing airways • Dulling of warning signs of low blood glucose levels • Constriction of small blood vessels • Sleep disturbance (nightmares) • Impotence • Indigestion

Sources

Prostaglandin Analogues- (Alm, Grierson, and Shields S93-S105)

Beta-blockers- ("Bupa"), ("Health Patient UK")