ORIGINAL ARTICLE

The efficacy of NHIS-listed anti-glaucoma drugs in the management of primary open-angle glaucoma

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Ghana is the most affected country in Africa as far as glaucoma is concerned. This study therefore aims at determining the efficacy of the National Health Insurance Scheme listed anti-glaucoma drugs in the management of primary open-angle glaucoma in Ghana. This retrospective survey was carried out at the Golden Jubilee Eye Centre of St Michael's Catholic Hospital, Pramso in the Bosomtwi Atwima Kwanwoma District of the Ashanti Region of Ghana from January 2008 to December 2010. By random and purposive sampling, 141 patient folders (35.25% of total folders studied) were selected and data on drugs and intra-ocular pressure measurements for eight consecutive visits to the centre were recorded and analyzed appropriately. The outcome of primary open-angle glaucoma in the study was not gender sensitive but increased with age (majority 70 – 79 years). While Timolol, in monotherapy, reduced but not significantly ($p > 0.05$) the initial mean intra-ocular pressure measurements, Latanoprost reduced the initial mean intra-ocular pressure very significantly ($p \leq 0.001$). Combination therapies involving Latanoprost and listed anti-glaucoma drugs reduced intra-ocular pressure significantly than combination therapies involving NHIS-listed drugs only ($p \leq 0.01$). Though the National Health Insurance Scheme listed anti-glaucoma drug show intra-ocular pressure reduction in mono- and combination therapies, reduction by Latanoprost and combination of Latanoprost with the NHIS-listed drugs is very much significant. An addition of Latanoprost to the National Health Insurance Scheme list of anti-glaucoma medications would therefore be very beneficial to glaucoma patients in Ghana.
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Keywords: Blindness, Intra-ocular pressure, Latanoprost, Timolol, Health Insurance Scheme

INTRODUCTION

Glaucoma is a group of disorders, principally optic neuropathy resulting from cupping and atrophy of the optic nerve head leading to visual loss and blindness (Khandekar *et al.*, 2008). It is often, but not always, associated with increased pressure in the eye (Rhee, 2008). Of these cardinal signs, visual field loss is diagnostically the most specific, since both cupping and intra-ocular pressure (IOP) exhibit

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physiological variations in a given population (Thylefors and Negrel, 1994).

Glaucoma is the second leading cause of blindness globally, after cataracts (Kingman, 2004; Nduaguba and Lee, 2006). Worldwide, an estimated 60.5 million people have glaucoma out of which 8.4 million have become blind. The prevalence is estimated to be on the increase and projected to affect 79.6 million people by the year 2020 (Gupta and Yülel, 2007). In Africa, glaucoma is the number one cause of irreversible blindness in most of its regions, and also Africa will have the highest ratio of glaucoma-to-adult population (Quigley and Broman, 2006).

Ghana is the most affected country in Africa and second in the world (Melamed *et al.*, 2010).

In anti-glaucoma therapy, a target pressure (approximately 19-22 mmHg) supposed to be the safest for the patient is set. Though there is no single IOP level that is safe for every patient, often, the aim is to achieve a pressure reduction of at least 30% from the initial (Rathore and Nema, 2009).

The National Health Insurance Scheme (NHIS), established under Act 650 of 2003 by the Government of Ghana as part of its services selected Acetazolamide, Betaxolol, Pilocarpine, and Timolol as the anti-glaucoma drugs to the healthcare needs of its registered clients. These drugs were chosen probably because of accessibility and lower cost. Latanoprost and Bimatoprost which are proven to have better IOP reduction effect (Zhang *et al.*, 2001), are not in the NHIS list. A meta-analysis of randomized controlled trials comparing Latanoprost with Timolol in the treatment of patients with open angle glaucoma suggests that Latanoprost is more effective than Timolol in lowering IOP (Zhang *et al.,* 2001). The mechanism of action and side effects of Pilocarpine and Acetazolamide limit their clinical use in glaucoma patients presenting with cataract and uveitis. This study therefore seeks to establish the efficacy of the NHIS-listed anti-glaucoma drugs in reducing IOP in primary open angle glaucoma and further serve as a guideline support base to practitioners in the prescription of anti-glaucoma medications.

MATERIALS AND METHODS
Study Design and Sampling Technique
This retrospective survey was carried out at the Golden Jubilee Eye Centre of St Michael's Catholic Hospital, Pramso in the Bosomtwi Atwima Kwanwoma District of the Ashanti Region, Ghana, from January 2008 to December 2010. Out of a total of 400 patients undergoing treatment for POAG at the facility during the study period, 141 folders for glaucoma patients with IOP measurements for at least eight (8) consecutive visits and receiving treatment were purposively sampled. Information on the age, gender, visual acuity, IOP measurements for eight (8) consecutive visits and drugs were recorded from patients' folder.

Ethical Clearance
Ethical clearance and approval for the study was given by the research and quality control unit of the facility.

Inclusion and Exclusion Criteria
Defaulting in the use of drugs, patients with other types of glaucoma, and patients who did not visit the clinic on monthly basis for eight successive visits were excluded from the study, limiting the sample size for this study from 400 to 141.

Data analysis
Data obtained from the folders were entered into the Statistical Package for Social Scientists (SPSS) for quantitative analysis. GraphPad Prism® Version 5.0 for Windows (GraphPad Software, San Diego, CA, USA) was used for statistical analyses and graphs of IOPs. Values plotted are mean ± SD of the percentage change in IOP and analyzed by One-way Analysis of Variance (ANOVA) followed by Dunnet's Multiple Comparison's test (post-hoc tests). The initial mean IOP recorded were used as the reference to which subsequent IOP changes were compared. $p \leq 0.05$ was considered statistically significant in all analysis.

$$\% \text{ change in IOP} = \frac{\text{Final IOP } - \text{ Initial IOP}}{\text{Initial IOP}} \times 100$$

RESULTS
A total of 141 patient data records were reviewed for POAG of which 75 (53.2%) were females and 66 (46.8%) were males. Their age range was between 30-100 years. Fifty four (38.3%) of the patients selected were aged 70-79; being the majority (Figure 1). Fifty (50) out of the 141 patient records had blurred vision as the initial complaint for reporting to the eye clinic (Figure 2).

Majority (62 out of 141; 43.97%) of the patients were observed to be on a three-drug combination therapy (Figure 3) involving Timolol-Pilocarpine-Acetazolamide (88.7%) and Timolol-Acetazolamide-Latanoprost (11.3%) (Figure 4C). Twenty eight
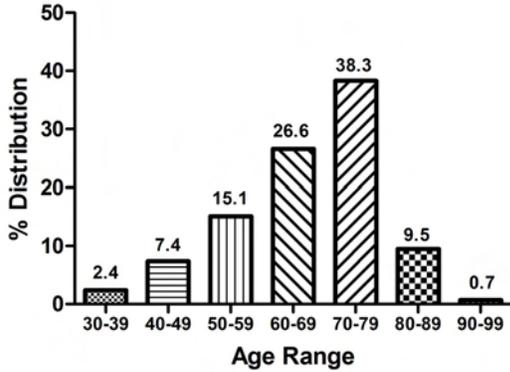
**Figure 1: The age distribution of the selected patients receiving treatment for POAG**
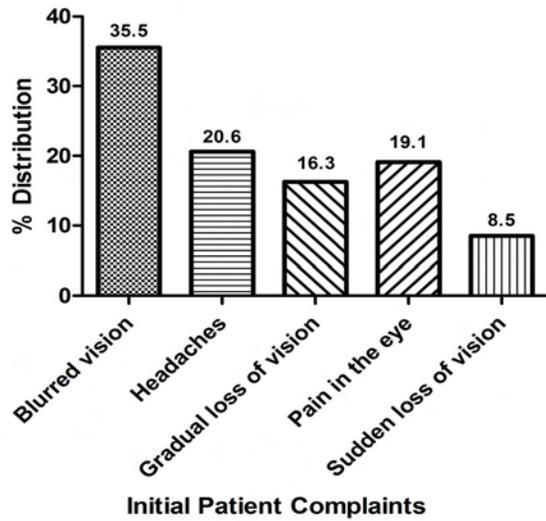
Figure 2: The initial patient complaints for reporting to the eye clinic

patients (19.85%) were on monotherapy (Figure 3) and used either Timolol (64.3%) or Latanoprost (35.7%) (Figure 4A) while 42 (29.78%) were on two-drug combination therapy involving Timolol-Pilocarpine (37.5 %), Timolol-Acetazolamide (50%), Timolol-Latanoprost (7.1%), or Pilocarpine-Acetazolamide (7.1%) (Figure 4B) with 9 (6.38%) were on Timolol-Pilocarpine-Acetazolamide-Latanoprost in a Four-Drug combination therapy.

While a total of 112 (79.43%) of the patients evaluated were on Timolol, Pilocarpine, and Acetazolamide in mono- or in combination therapies, only 29 (20.56%) were on therapies involving Latanoprost. It was observed that up to 65 (58.03%) of the patients on mono/combination therapies involving Timolol, Pilocarpine, and Acetazolamide were later on withdrawn from these for uncontrolled IOP, or due to reactions and adverse effects from these drugs.

Individuals on Timolol in monotherapy, experienced significant reductions ($p \leq 0.05$) in the initial
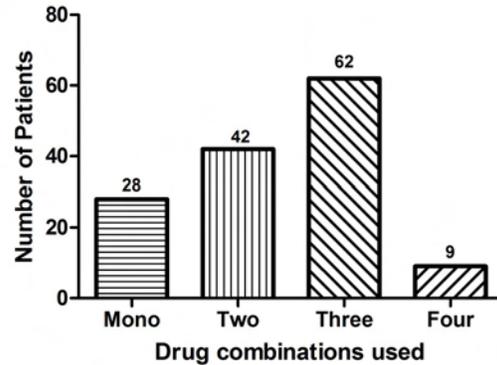
Figure 3: Patients on monotherapy, two, three, and four-drug combination therapy

mean IOP from the second visit to the eighth visit ($p \leq 0.05$) (Figures 5A). Patients on Latanoprost also experienced significant reduction ($p \leq 0.05$) from the second visit and by the eighth visit, IOP reduction was very significant ($p \leq 0.001$) (Figure 5B). Latanoprost reduced IOPs to between 19-22 mmHg (the target for the end-of-treatment), however, Timolol did not achieved this target. The percentage reduction in initial mean IOPs after the eighth visit in patients using latanoprost was between $47.2 \pm 21.6\%$ and $48.8 \pm 15.8\%$ in the right and left eyes respectively. This percentage reduction was far higher compared to Timolol users which were between $12.9 \pm 22.5\%$ and $19.6 \pm 20.9\%$ (Figure 9A).
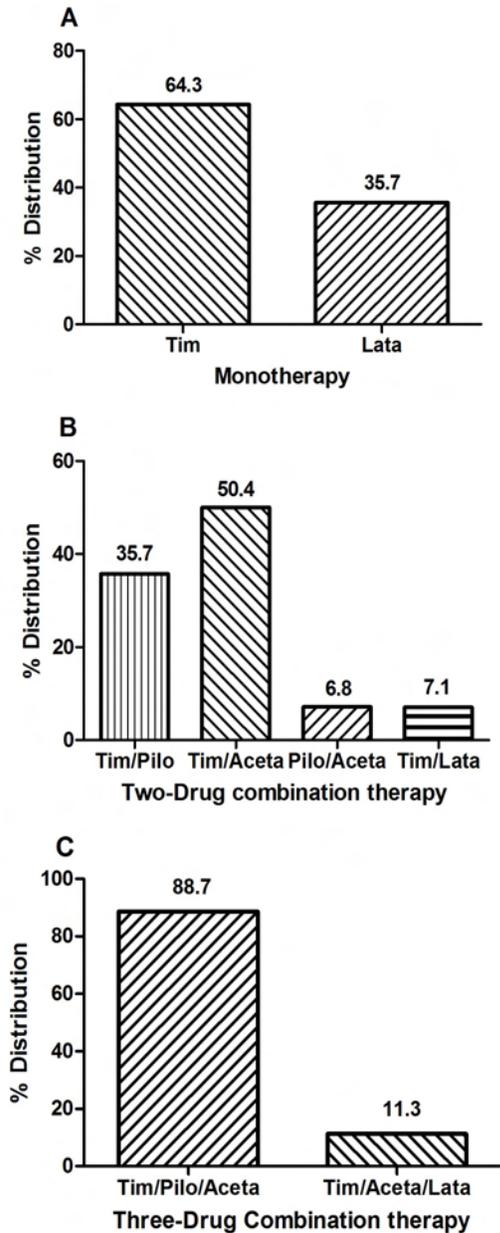
Figure 4: A. Details of patients on monotherapy. B. Details of patients on two-drug combination therapy. C. Details of patients on three-drug combination therapy. Tim = timolol; Pilo = Pilocarpine; Aceta = Acetazolamide; Lata = Latanoprost.
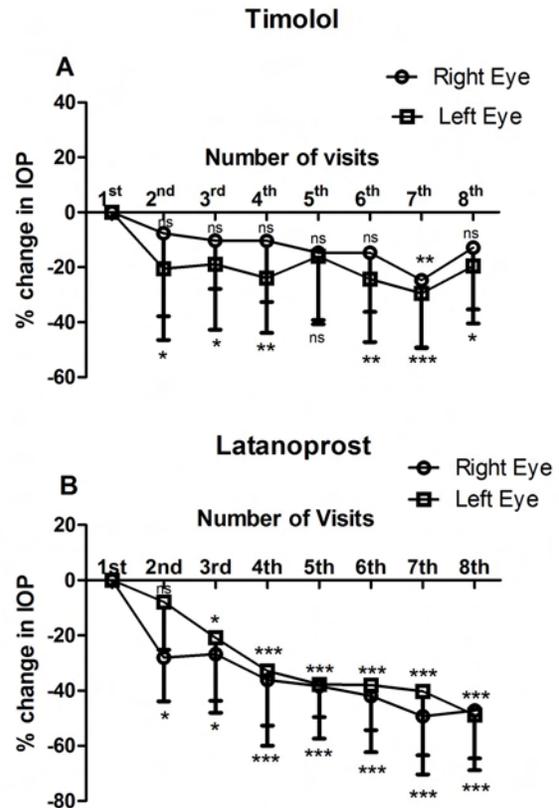

Figure 5: The change in initial IOP value caused by (A) Timolol 0.5 % (n=18); (B) Latanoprost (n=10) in monotherapy in POAG patients for eight consecutive clinic visits. Values plotted are mean ± SD (n=28). Significant differences between the initial IOP and consecutive visits were analyzed using ANOVA followed by Dunnett's *post hoc* test. *$P \leq 0.05$; ** $P \leq 0.01$; ***$P \leq 0.001$.

When monotherapy fails to significantly lower IOP, combination therapy is sought for. In this study, it was observed that Timolol-Pilocarpine, Timolol-Acetazolamide, and Pilocarpine-Acetazolamide combinations did not reduce significantly initial mean IOPs (in both eyes) of patients on these combinations throughout the eight consecutive visits (Figures 6A, 6B, and 6D. Timolol-Latanoprost combination therapy however, significantly de-

creased (p ≤ 0.05) the initial mean IOP in both eyes from the third visit and by the eighth visit the decrease was very significant (p ≤ 0.001) (Figure 6C) with a percentage reduction of 63.7 ± 1.6% in the right eye and 61.4 ± 10.6% in the left eyes (Figure 9B). Timolol-Latanoprost combination therapy thus achieved the treatment target of reducing IOPs.

In the Timolol-Pilocarpine-Acetazolamide and Timolol-Acetazolamide-Latanoprost combination therapy, there were significant decrements (p ≤ 0.01) in initial mean IOP in both eyes from the fourth visit to the eighth. The differences in percentage reduc-

tion in initial mean IOP between these two three-drug combination therapies after the eighth visit which were 22.2 ± 29.3% in the right and 22.2 ± 31.3% in the left, and 32.00 ± 14.8% and 30.4 ± 18.4% respectively (Figure 9C) were not significantly different (p > 0.05), indicating similar efficacy in the three-drug combination therapies. The Timolol-Pilocarpine-Acetazolamide-Latanoprost combination therapy significantly decreased (p ≤ 0.01) initial mean IOP in both eyes after the eight consecutive visits (Figure 8) with the IOP reducing by 33.6 ± 19.6% and 29.8 ± 18.00% in the right and left eye respectively.
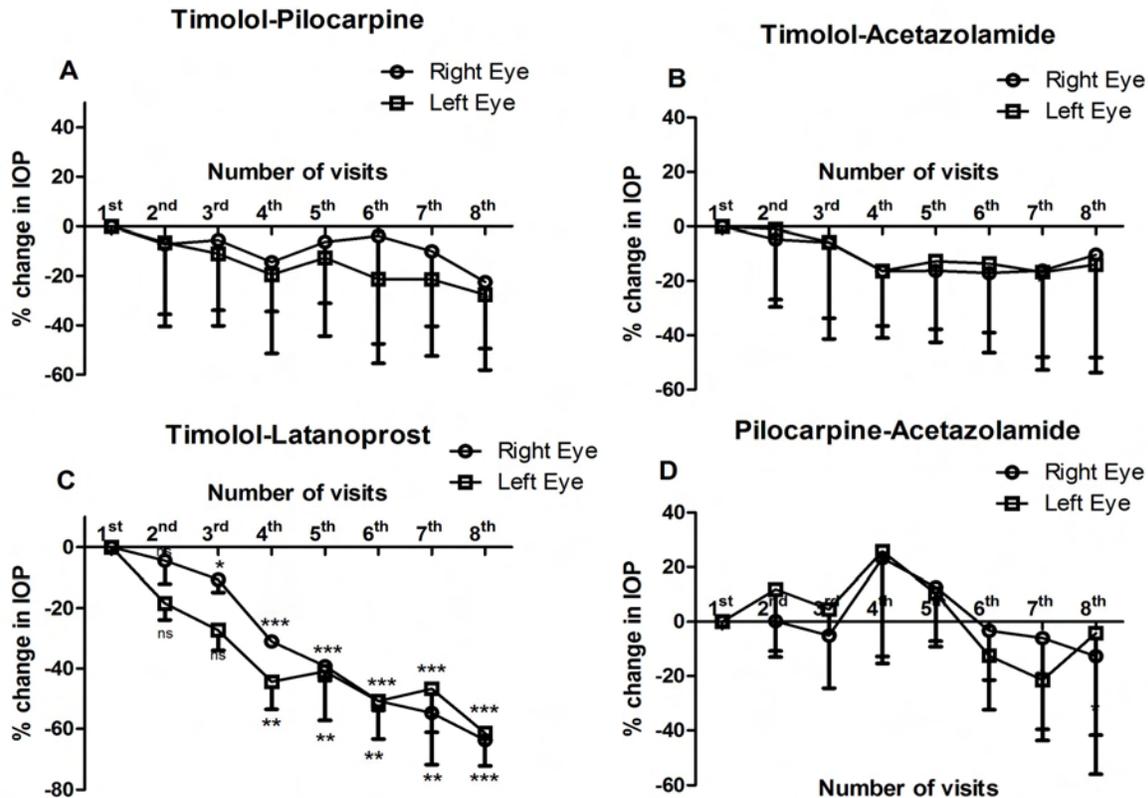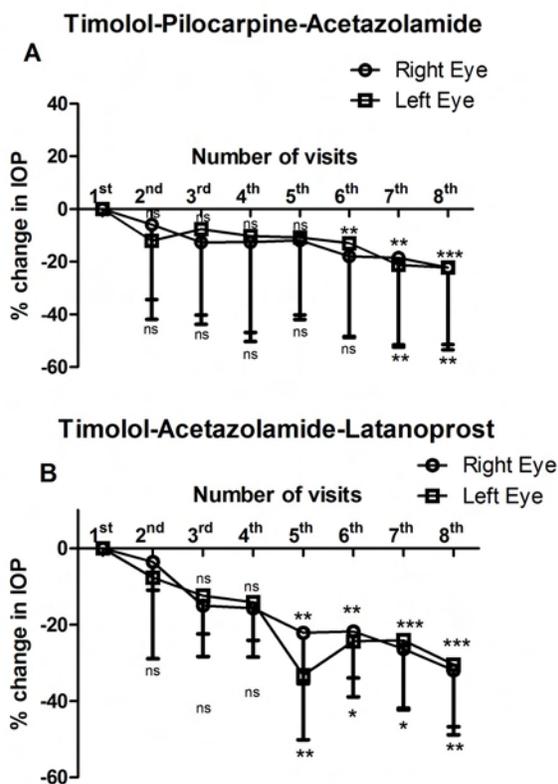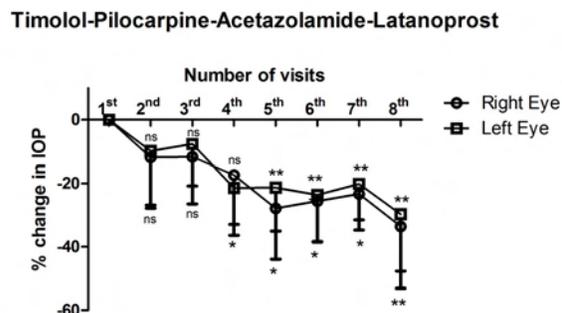

Figure 6: The change in initial IOP value caused by (A) Timolol-Pilocarpine (n=15); (B) Timolol-Acetazolamide (n=21); (C) Timolol-Latanoprost (n=3); and (D) Pilocarpine-Acetazolamide (n=15) in a two-drug combination therapy in POAG patients for eight consecutive clinic visits. Values plotted are mean ± SD (n=42). Significant differences between the initial IOP and consecutive visits were analyzed using ANOVA followed by Dunnett's *post hoc* test. ns *P* > 0.05; **P* ≤ 0.05; ** *P* ≤ 0.01; ***P ≤ 0.001.

Figure 7: The change in initial IOP value caused by (A) Timolol-Pilocarpine-Acetazolamide (n=55) and (B) Timolol-Acetazolamide-Latanoprost (n=7) in a three-drug combination therapy in POAG patients for eight consecutive clinic visits. Values plotted are mean ± SD (n=62). Significant differences between the initial IOP and consecutive visits were analyzed using ANOVA followed by Dunnett's *post hoc* test. ns $P > 0.05$; * $P \leq 0.05$; ** $P \leq 0.01$; ***$P \leq 0.001$.

Figure 8: The change in initial IOP value caused by Timolol-Pilocarpine-Acetazolamide-Latanoprost (n=9) in a four-drug combination therapy in POAG patients for eight consecutive clinic visits. Values plotted are mean ± SD (n=9). Significant differences between the initial IOP and consecutive visits were analyzed using ANOVA followed by Dunnett's *post hoc* test. ns $P > 0.05$;*$P \leq 0.05$; ** $P < 0.01$.

DISCUSSION

The study was to determine the efficacy of the National Health Insurance Scheme listed anti-glaucoma drugs in lowering intra-ocular pressure to slow optic nerve damage and decreasing the rate of vision loss in primary open-angle glaucoma patients. Patients aged 70-79 were in the majority confirming the association of age as a risk factor in primary open angle glaucoma (Friedman *et al.*, 2006; Stamper *et al.*,

2009). However, this does not infer strictly that the disease is limited to the elderly as it occurs in young adults as well (Stamper *et al.,* 2009) confirmed by the age distribution observed with this study. The effect of age on the prevalence of POAG holds true even after compensating for the relationship between increasing age and increased IOP.

Individuals on Timolol as monotherapy were in the majority, confirming other studies where Timolol was also found to be the frequently prescribed drug for POAG (Sharma *et al.*, 2007). However the reduction in initial mean IOP cause by Timolol could not match-up with that caused by the brands of Latanoprost which achieved more than 30% reduction in initial mean IOP (Rathore and Nema, 2009) confirming previous studies where Timolol was less effective than Latanoprost (Mishima *et al.*, 1996).

Timolol inhibits the production of aqueous humor achieved mainly by blockade of β2-adrenoceptors on nonpigmented epithelial cells of the ciliary body with a subsequent reduction in IOP (Sharma *et al.,* 2007). Latanoprost causes an increase in uveoscleral

outflow (Huq, 2007) caused by elevated presence of *metalloproteinase*, which break down the collagen matrix within the uveoscleral region surrounding the ciliary muscle bundles. New channels for aqueous outflow are created (in addition to the drain in the trabecular meshwork), boosting uveoscleral outflow to greater than 50% of total flow from the eye. This makes the prostaglandin analogues better IOP reducers than the β-blockers. This therefore confirms the fact that prostaglandin analogues have become the primary agent for therapy (Fingeret, 2009), and Timolol should be used less often in a primary role. However, all the various brands of Latanoprost are expensive making it difficult for patients to acquire and use; a setback to it being the primary agent of therapy. This therefore should be a reason for Latanoprost to be incorporated into the NHIS list of anti-glaucoma drugs.

With more complicated situations of glaucoma coupled with inflammatory disorders of the eye (triggered by reactive oxygen species and oxidative stress due to aging) and tolerance to drugs, monotherapy is not effective and combination of anti-glaucoma drugs are then applied to give a synergistic effect. It is therefore expected that the percentage reduction in initial mean IOPs would increase significantly with the two-drug, three-drug and four-drug combination therapies over that for monotherapy. The Timolol - Latanoprost combination reduced very significantly initial mean IOP compared to the other two-drug combination therapies. This combination would cause a significant reduction in aqueous production and a much more enhanced elimination of aqueous (through the drains in the trabecular meshwork and uveoscleral outflow).

There were good IOP reductions with the use of three-combination anti-glaucoma therapies involving Latanoprost though differences in IOPs reduction between these and other three-drug combination therapies were not significant. The four-drug combination therapy was also found to be effective. The Timolol-Acetazolamide-Pilocarpine-Latanoprost combination significantly reduced the initial mean IOP between 29 - 34%. This may delay optic nerve damage, progressive visual field loss and blindness
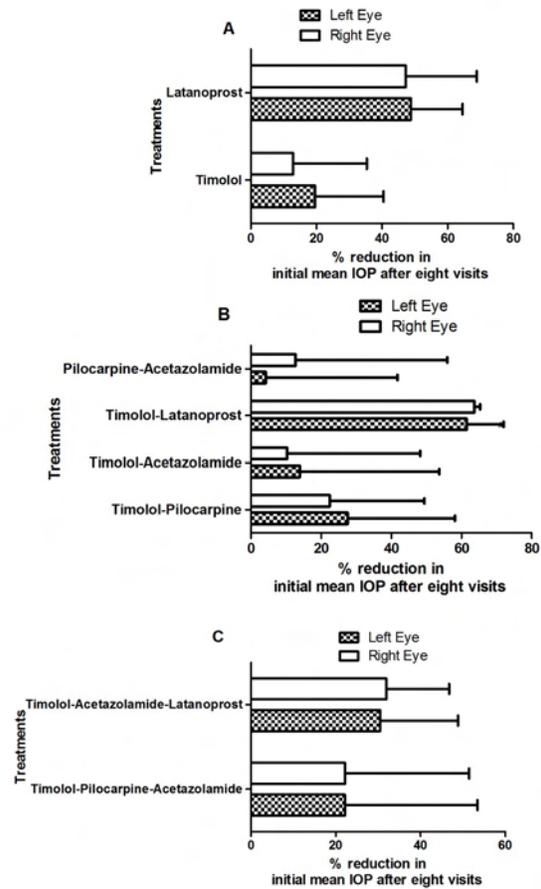
Figure 9: The differences in percentage reduction in initial IOP after eight successive visits caused by NHIS-listed anti-glaucoma drugs in mono- and/or combination therapy as against Latanoprost alone or Latanoprost in combination with NHIS-listed anti-glaucoma drugs after eight successive visits. Values plotted are mean ± SD.

(Rathore and Nema, 2009).

Ocular complications interfere with drug activity. Patients with cataract and uveitis on antiglaucoma therapy could experience various adverse reactions that may not enhance patient compliance to therapy. Both cataracts and glaucoma can be a natural part of the aging process and many people over 60 may have both. Cataract patients on Pilocarpine

may find their vision lowered. This medication tends to shrink the pupil, which lowers the amount of light entering the eyes. Since cataracts may already be clouding vision, this may make vision worse and therefore patients may not comply with Pilocarpine therapy (Sakamoto, 2011). Up to 20% of patients with uveitis will develop glaucoma (Panek *et al.,* 1990). Therefore if glaucoma exists already, this inflammatory condition makes it worse.

Patients on mono/combination therapies involving Timolol, Pilocarpine, and Acetazolamide were later on withdrawn from these for uncontrolled IOP, or due to reactions and adverse effects to these drugs. The pharmacodynamics of Pilocarpine and Acetazolamide has been found to vary with the age of patients with POAG (Bartlett and Jaanus, 2006). Patients above forty years may not benefit so much from these drugs. Aging comes with constriction of the pupils (senile miosis) and Pilocarpine, a miotic agent (parasympathomimetic), which works by contraction of the ciliary muscle, tightening the trabecular meshwork and allowing increased outflow of the aqueous may not be possible because the pupil cannot be constricted beyond a certain limit and so the IOP may not be reduced significantly. Acetazolamide causes reduction of body potassium, numbness or tingling sensations in the arms and legs (more pronounce with ageing) therefore patients' compliance is questionable which does not augur well for effective therapy. Some conditions such as cataract and uveitis among others in the glaucoma patients do not benefit from Pilocarpine usage due to the mechanism of action and side effects of these drugs. Male patients especially complain about excessive urination at night, tingling of the extremities and impotence with the use of Acetazolamide.

CONCLUSIONS
Though the National Health Insurance Scheme listed anti-glaucoma drug showed intra-ocular pressure reduction in mono- and combination therapy, reduction by Latanoprost and combination of Latanoprost with the listed drugs is very much significant. An addition of Latanoprost to the list of anti-glaucoma medications would be essentially beneficial.

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