Study of the efficacy and safety of once and twice daily timolol (0.5% solution) treatment in controlling intraocular pressure

Kergeda MO, Alemu AM

Department of Ophthalmology, Faculty of School of Medicine, Addis Ababa University, College of Health Sciences, Addis Ababa, Ethiopia

Corresponding author: Dr. Muhidin Oumer Kergeda, Department of Ophthalmology, Faculty of School of Medicine, Addis Ababa University, College of Health Sciences, Addis Ababa, Ethiopia. Email: barcho7@gmail.com

ABSTRACT

Objective: To compare the efficacy and safety of once-daily versus twice-daily 0.5% timolol ophthalmic solution in reducing Intraocular Pressure (IOP) among patients with mild to moderate open-angle glaucoma or ocular hypertension.

Methods: A prospective comparative interventional study was conducted at a tertiary referral hospital from November 2022 to September 2023. Eighty-four patients were allocated to once-daily or twice-daily 0.5% timolol treatment using a quasi-randomization method (initial lottery followed by alternate allocation). Baseline IOP was measured at 8:00am, 12:00pm, and 4:00pm, together with pulse rate and blood pressure. Measurements were repeated after one month. Data were analyzed using SPSS version 26, with $p < 0.05$ considered statistically significant.

Results: Both groups demonstrated significant reductions in IOP from baseline (once daily: $p \leq 0.004$, 95% CI: 1.23–5.96 mmHg; twice daily: $p \leq 0.001$, 95% CI: 1.63–5.75 mmHg). However, there was no statistically significant difference in IOP reduction between the two groups. Systemic and ocular adverse effects were also comparable between the treatment groups.

Conclusion: The findings suggest that once-daily 0.5% timolol may be as effective and safe as twice-daily treatment for patients with mild to moderate open-angle glaucoma or ocular hypertension.

Key words: Timolol, Intraocular pressure, Glaucoma, Ocular hypertension, Beta-blocker, Eye drops, Dosing frequency, Adverse effects

INTRODUCTION

Glaucoma is a group of progressive optic neuropathies characterized by an excavated optic disc, loss of retinal ganglion cells, and corresponding visual field loss[1]. It is a leading cause of irreversible blindness worldwide, with elevated intraocular pressure as the main risk factor. Anti-glaucoma medications lower IOP by affecting aqueous humor dynamics, with nonselective β-blockers taken once or twice daily[1,2]. Timolol maleate reduces aqueous humor production by 20–50% and lowers IOP by 18–25%, but may cause ocular and systemic side effects, including bradycardia, hypotension, and bronchospasm[1,3].

Nighttime or anaesthesia reduces aqueous humor production by 50%, similar to daytime adrenergic blockers[1,2]. Timolol once or twice daily shows comparable efficacy and safety, this study evaluates 0.5% timolol dosing in Ethiopian patients[3].

Objective: In Ethiopia, ophthalmologists commonly prescribe 0.5% timolol twice daily for glaucoma management. However, evidence regarding whether once-daily administration provides comparable efficacy with fewer side effects in Ethiopian patients is limited. Since reduced dosing frequency may improve patient adherence, reduce systemic adverse effects, and lower treatment costs, this study was conducted to evaluate the efficacy and safety of 0.5% timolol when used twice daily versus once daily among Ethiopian patients.

Rationale: Using the minimum effective number of medications with the lowest effective dosing frequency may reduce patient burden, improve adherence, and consequently help control disease progression more effectively. Although timolol 0.5% is commonly prescribed either once or twice daily, there is limited local evidence comparing the efficacy of these two dosing regimens among Ethiopian patients. Therefore, this study was conducted to evaluate whether once-daily timolol provides a comparable intraocular pressure-lowering effect to twice-daily treatment. If similar efficacy is achieved with once-daily dosing, it may improve patient convenience, adherence, and overall quality of life.

Literature: Besides, many studies in the literature have shown that there is no significant difference in intraocular pressure reduction or tolerability of timolol when administered once daily versus twice daily in different

formulations. Similar findings have been reported in both parallel-group and crossover studies.[4–9].

MATERIALS AND METHODS

Study design: This study was a prospective comparative interventional study conducted to compare the efficacy and safety of once-daily versus twice-daily 0.5% timolol ophthalmic solution among patients with glaucoma and ocular hypertension. Participants were followed prospectively after initiation of treatment. An alternate assignment after an initial lottery method was used, in which the treatment assignment for the first participant was determined by lottery method, after which subsequent participants were assigned alternately to the two treatment groups until the required sample size was achieved. It was conducted at a tertiary referral hospital from November 2022 to September 2023.

Ethical considerations: Ethical approval for this study was obtained from the Institutional Review Board of a university in Ethiopia (Approval No: 089/22/Optha). Written informed consent was obtained from all participants before enrollment in the study, and the study adhered to the principles of the Declaration of Helsinki.

Masking: This study employed single masking at the outcome assessment level. The nurses who measured intraocular pressure were masked to participants' treatment allocation in order to minimize measurement bias. Participants received their assigned treatment regimen according to the study protocol, while the principal investigator and co-authors were not masked during study implementation and data collection. This has been acknowledged as a potential limitation of the study.

Sample size determination: Sample size was calculated using G*Power version 3.1.9.4 based on an independent t-test. The input parameters were: effect size (p) = 80%, alpha error probability = 5%, and power (1–β) = 95%, derived from similar literature. This yielded a sample size of 35 participants per group. After adding a 15% non-response rate, the final sample size was 42 per group, giving a total sample size of 84.

Inclusion criteria: Patients diagnosed with mild to moderate Open-Angle Glaucoma (OAG) or ocular hypertension, with IOP below 35mm Hg, who had not started any anti-glaucoma medication or had discontinued it for more than six weeks were included.

Exclusion criteria: On the contrary, excluded patients were those who had undergone ocular surgery, had angle-closure glaucoma, ocular trauma or inflammation, were taking systemic or local medications that could affect IOP like systemic B-blockers, cardiac patients taking medications, those on steroids, patients with bronchial asthma, those allergic to beta-blockers, patients with poor medication adherence, or those with corneal opacity affecting IOP measurement.

Participants: The diagnosis of glaucoma and its subtypes were confirmed. The diagnosis of these glaucoma types was made by ophthalmologists who were not part of the study authors after performing the necessary clinical evaluations and investigations required for diagnosis. The role of the study authors was to recruit patients after confirming that they fulfilled the inclusion and exclusion criteria of the study. A total of 84 patients meeting the inclusion criteria were recruited. Participant's flow chart is shown in results section.

Randomization: A quasi-randomization allocation method was used. The treatment group for the first participant was determined by lottery method, after which subsequent participants were assigned alternately to the once-daily timolol 0.5% group or the twice-daily group until the total sample size of 84 participants (42 in each group) was achieved. Participants excluded or lost due to poor adherence were replaced, and the alternate allocation sequence was continued.

Intervention: The study consisted of two groups: an intervention (once-daily timolol 0.5%) group and a comparison (twice-daily timolol 0.5%) group. The intervention was the administration of 0.5% timolol ophthalmic solution, with participants assigned to either once-daily or twice-daily dosing. Both groups received the same formulation, and the only difference between them was the frequency of administration.

Procedure: Baseline IOP, Blood Pressure (BP), and Pulse Rate (PR) measurements were recorded. The IOP measurements were taken on the same day at 8:00am, 12:00pm, and 4:00pm, while BP and PR were measured solely at 8am. The IOP measurements were consistently monitored throughout the study using the I-Care100-tonometer model TOA11**.** Trained glaucoma clinic nurses used the digital measuring device to measure BP and PR for all patients. All measurements were conducted with patients in a sitting position. Each patient and family member was explained the procedure for administering the eye drops. They were also instructed to adhere to the medication regimen strictly. Both groups received the same brand of timolol 0.5% solution from the principal investigator. The once-daily group was advised to apply their medication at 9:00 am, whereas the twice-daily group was instructed to apply the same medicine at 9:00am and 9:00pm.

If a patient was diagnosed with bilateral OAG or ocular hypertension, they were advised to use the medication for

both eyes. However, for the study purpose, the eye with the higher average IOP at the three baseline measurements was selected as the study eye.

Baseline measurements and examination were repeated after one-month treatment period, employing the same procedure. Ocular examination and systemic review for possible adverse effect evaluation was done by the principal investigator. The questionnaire was developed for this study and filled out by principal investigator for all patients

Adherence and monitoring: Adherence was actively monitored throughout the one-month treatment period using a patient-administered medication checklist. Each patient was instructed to record every instillation of the prescribed Timolol dose daily. At the end of the study period, patients returned their completed checklists for evaluation.

Adherence was assessed by calculating the percentage of missed doses using the formula: (number of missed doses ÷ total expected doses) × 100. Patients with more than 15% missed doses were considered non-adherent, excluded from the final analysis, and replaced to maintain the required sample size. Only adherent patients were included in the primary outcome analysis. This approach ensured objective monitoring of adherence and minimized bias in the evaluation of intraocular pressure outcomes.

Primary and secondary outcomes: The primary outcome of the study was to compare the mean difference in Intraocular Pressure (IOP) reduction and safety between the once-daily and twice-daily 0.5% Timolol groups after one month of treatment.

The secondary outcomes included the mean IOP reduction within each treatment group, treatment adherence, differences in IOP reduction among glaucoma subtypes. Adherence was assessed based on compliance with the prescribed dosing regimen, and safety was evaluated by the occurrence of ocular and systemic side effects associated with timolol use.

Statistical analysis

The data were checked for completeness and consistency and then entered into SPSS version 26. Normality of continuous variables was assessed using the Shapiro–Wilk test and Q–Q plots. The IOP measurement data were approximately normally distributed ($p > 0.05$), whereas the PR, SBP, and DBP data were not normally distributed ($P<0.05$)). Accordingly, parametric tests were applied where normality assumptions were met, and non-parametric tests were used when the assumptions were violated.

Descriptive statistics were used to summarize baseline characteristics and outcome variables. The primary analysis compared mean Intraocular Pressure (IOP) reduction and safety between the once-daily and twice-daily Timolol groups using an independent sample t-test and Chi-square test, respectively. The mean difference in IOP reduction between groups was reported with its 95% confidence interval as a measure of effect size.

Within-group comparisons of baseline and post-treatment IOP were performed using paired samples t-tests. A one-sample t-test was used to compare the mean IOP reduction in each study group with the expected average IOP reduction (18%–25%). One-way ANOVA was used to assess differences in IOP reduction among glaucoma subtypes.

The Wilcoxon signed-rank test was used to assess the effect of timolol treatment on Pulse Rate (PR), Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP), while the Mann–Whitney U test was used to determine differences between the two treatment groups with respect to PR, SBP, and DBP.

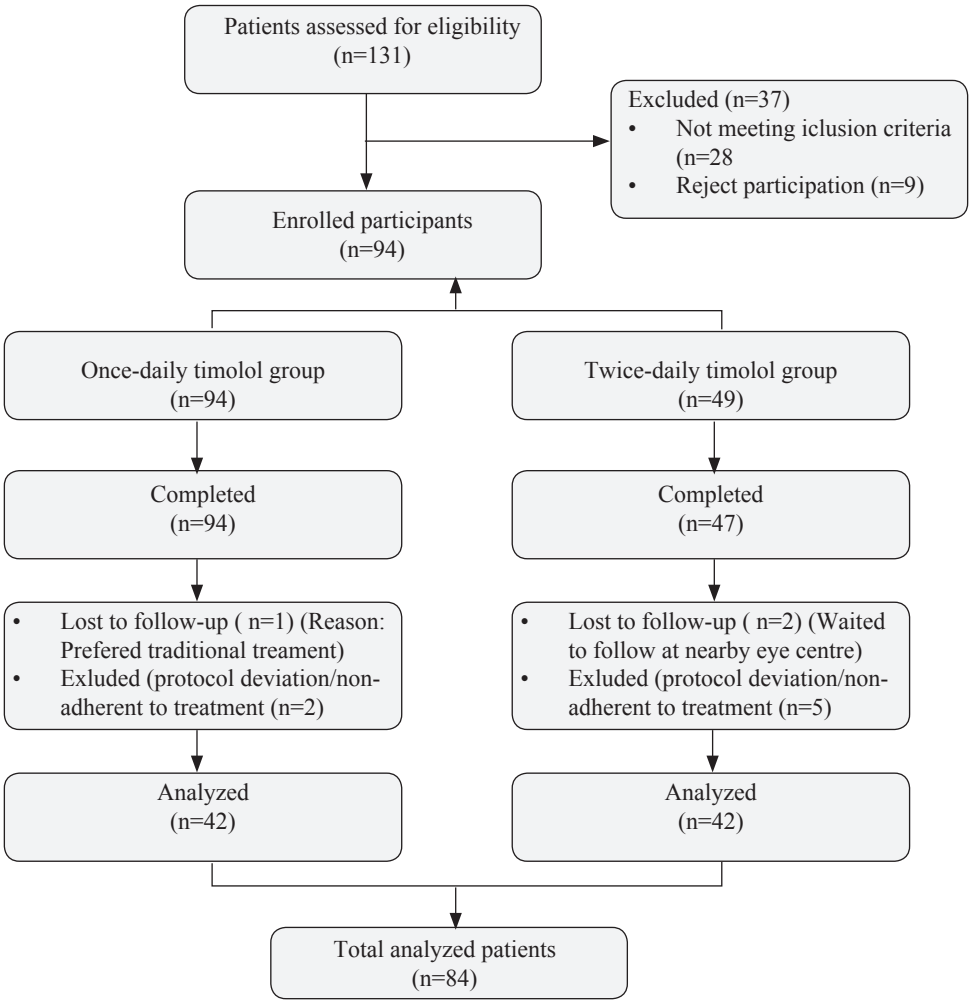
Chi-square test was used for categorical variables such as adherence and side effects. Risk ratios with 95% confidence intervals were calculated for categorical outcomes where appropriate. A p-value of less than 0.05 was considered statistically significant.

Operational definitions

(a) Open-angle glaucoma was defined as glaucomatous optic nerve damage with corresponding visual field defects and an open angle on gonioscopy.
(b) Ocular hypertension was defined as an intraocular pressure greater than 21 mmHg without glaucomatous optic nerve damage or visual field loss.
(c) Primary open-angle glaucoma was defined as the presence of glaucomatous optic neuropathy with corresponding visual field defects, open anterior chamber angles on gonioscopy, and elevated intraocular pressure and absence of secondary causes.
(d) Pseudoexfoliative glaucoma was defined as glaucoma associated with pseudoexfoliative material deposition on anterior segment structures in the presence of glaucomatous optic nerve damage and open angles.
(e) Normal-tension glaucoma was defined as glaucomatous optic nerve damage and corresponding visual field defects with intraocular pressure within the statistically normal range (<21 mmHg).
(f) The severity of glaucoma was classified based on the Vertical Cup-To-Disc Ratio (VCDR), where a VCDR of less than 0.65 was considered mild glaucoma, a VCDR between 0.65 and 0.85 was considered moderate glaucoma, and a VCDR greater than or equal to 0.85 was considered severe glaucoma.
(g) A participant was considered hypertensive if the systolic blood pressure was greater than or equal to 140 mmHg and/or the diastolic blood pressure was greater than or equal to 90 mmHg.

RESULTS

Participant flow chart



Most of the patients were males, accounting for more than 50% of the cases. The mean age was 68 and 56 in once daily and twice daily groups, respectively (Table 1).

Table 1: Background characteristics of the study participants.2023 (N=84)

Characteristics	Once daily group No. (%)	Twice daily group No. (%)
Number of patients	42	42
Sex		
Female	12 (28.6%)	18 (42.9%)
Male	30 (71.4%)	24 (57.1%)
Age group (years)	40-82	28-80
Mean age	68.3	56.5
Hypertensive patients	22 (52.4%)	18 (42.9%)
Baseline mean PR	81.5 (63-126)	80 (57-109)
Glaucoma type		
PXG	30 (71.4%)	15 (35.7%)

POAG	9 (21.4%)	14 (33.3%)
NTG	0	2 (4.8%)
OHT	3 (7.1%)	11 (26.2%)
Adherence	42/44*100 (93.33%)	42/47*100 (89.36%)

†PXG = Psudoexfoliative Glaucoma; POAG = Primary Open Angle Glaucoma; NTG = Normal Tension Glaucoma; OHT = Ocular Hypertension; PR = Pulse Rate

Table 2: Mean baseline intraocular pressure (IOP) measurements at 8:00am, 12:00pm, and 4:00pm

Report				
1. Twice daily group 2. Once daily group		Baseline IOP at 8:00am	Baseline IOP at 12:00pm	Baseline IOP at 4:00pm
1.00	Mean	23.2619	22.9048	23.0238
	N	42	42	42
	Std. Deviation	6.16465	4.87807	5.18200
2.00	Mean	20.2857	21.6190	20.2619
	N	42	42	42
	Std. Deviation	5.72238	6.30119	5.99618
Total	Mean	21.7738	22.2619	21.6429
	N	84	84	84
	Std. Deviation	6.09829	5.63791	5.74067

The average baseline IOP of all study participants at 8:00am, 12:00pm and 4:00pm was 21.7738 mmHg, 22.2619 mm Hg, and 21.6429 mm Hg, respectively.

Table 3: Post treatment mean IOP & mean IOP-deference measurements at 8:00am, 12:00pm, and 4:00pm

Report							
1. Twice daily group 2. Once daily group		Post treatment IOP at 8:00am	Post treatment IOP at 12:00pm	Post treatment IOP at 4:00pm	Mean IOP_ diff 8:00am	Mean IOP_ diff 12:00pm	Mean IOP diff. 4:00pm
1.00	Mean	19.5714	18.9524	19.2381	3.6905	3.9524	3.7857
	N	42	42	42	42	42	42
	Std. Deviation	5.72603	5.77612	5.19761	6.60188	5.56536	6.47899
2.00	Mean	17.0952	16.6905	16.6905	3.1905	4.9286	3.5714
	N	42	42	42	42	42	42
	Std. Deviation	7.36773	7.81646	6.61295	6.31390	6.05017	7.50331
Total	Mean	18.3333	17.8214	17.9643	3.4405	4.4405	3.6786
	N	84	84	84	84	84	84
	Std. Deviation	6.67550	6.92500	6.04889	6.42538	5.79853	6.96836

The average post treatment mean IOP of all study participants at 8:00am, 12:00pm, and 4:00pm was 18.3333 mmHg, 17.8214 mmHg, and 17.9643 mmHg, respectively.

Once- daily group

The mean baseline IOP in this group was 20.7222 mmHg. After one month of treatment, the mean IOP was reduced to 16.8254 mmHg. Pretreatment mean pulse, systolic, and diastolic BP values were 81.5714, 146.0476 mmHg, and 78.3810 mmHg, respectively. The post-treatment values were 79.8571, 145.3571 mmHg, and 80.2143 mmHg. The mean reduction of intraocular pressure with once-daily timolol was from 12.8985 to 22.5857%.

A one-sample t-test was conducted to compare the mean percentage reduction achieved with once-daily timolol treatment against the expected minimum percentage reduction of 18%. The analysis showed no statistically significant difference at any of the three time points. The p-values for the 8:00am, 12:00pm, and 4:00pm measurements were 0.377, 0.218, and 0.402, respectively.

Table 4: Intraocular pressure values of once- daily timolol treatment, 2023 (N=42)

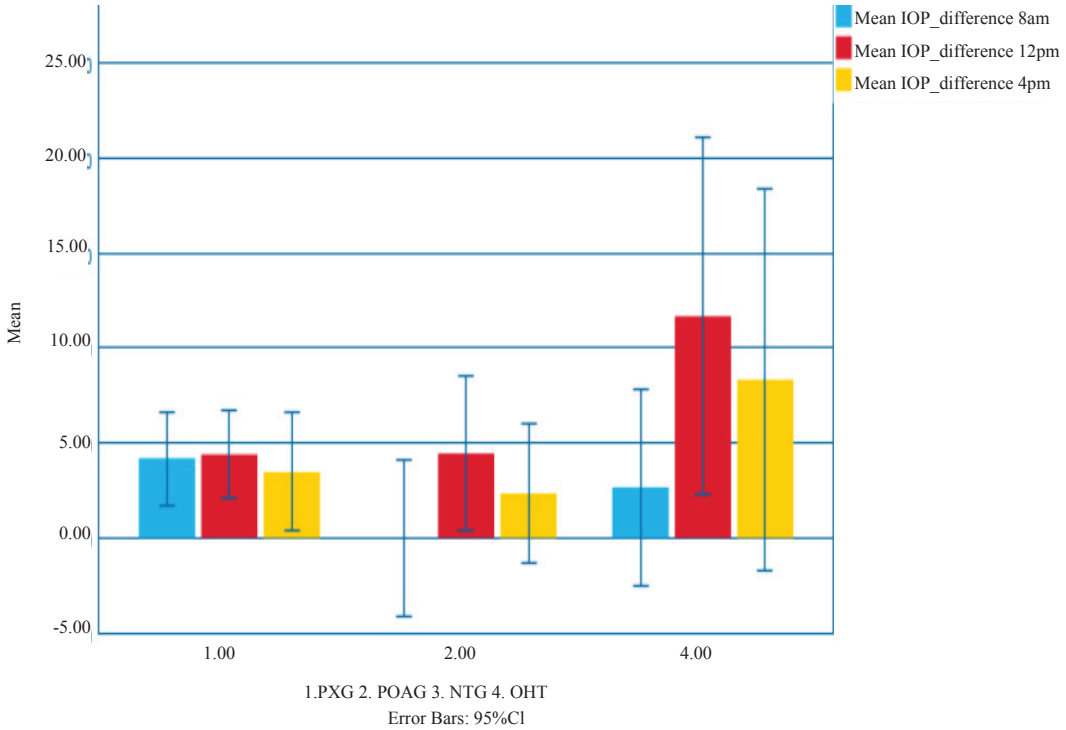
Paired Samples Test[a]

Mean		Paired Differences				t	df	Sig. (2-tailed)
		Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1	Baseline IOP at 8:00am – post treatment OP at 8:00am	3.19048	6.31390	.97426	1.22293	5.15802	3.275	41	.002
Pair 2	Baseline IOP at 12:00pm - post treatment IOP at 12:00pm	4.92857	6.05017	.93356	3.04321	6.81394	5.279	41	.000
Pair 3	Baseline IOP at4 pm - post treatment IOP at 4pm	3.57143	7.50331	1.15779	1.23323	5.90962	3.085	41	.004

a. 1. Twice daily group 2. Once daily group = 2.00

The effect of once daily timolol eye drop treatment in intraocular pressure lowering on subtypes of OAG or ocular hypertension was higher in ocular hypertension and lower in primary OAG patients, but this was not statistically significant (Figure 1 and Table 5).

Figure 1: Effect of once- daily timolol treatment on type of OAG and OHT at the three timings



**OHT = Ocular Hypertension; OAG = Open Angle Glaucoma; NTG = Normal Tension Glaucoma; PXG = Psudoexfoliative Glaucoma; POAG = Primary Open Angle Glaucoma; IOP = Intraocular Pressure

Table 5: Comparison of mean intraocular pressure reduction at 8:00am, 12:00pm, and 4:00pm among glaucoma subtypes

1. Twice daily 2 Once daily group = 2.00-ANONA-May 16,2026

ANOVA[a]

		Sum of Squares	df	Mean Square	F	Sig.
meanIOP_difference8am	Between Groups	123.010	2	61.505	1.587	.217
	Within Groups	1511.467	39	38.756		
	Total	1634.476	41			
meanIOP_difference12pm	Between Groups	146.697	2	73.348	2.113	.135
	Within Groups	1354.089	39	34.720		
	Total	1500.786	41			
meanIOP_difference4pm	Between Groups	82.152	2	41.076	.720	.493
	Within Groups	2226.133	39	57.080		
	Total	2308.286	41			

a. 1. twice daily group 2. once daily group = 2.00

††

The Wilcoxon signed-rank test showed no statistically significant difference in Pulse Rate (PR), Systolic Blood Pressure (SBP), or Diastolic Blood Pressure (DBP) after once daily timolol treatment, with p-values of 0.485, 0.891, and 0.129, respectively.

Twice- daily group

The mean baseline IOP in this group was 23.0635.9 mmHg. After one month of treatment, it decreased to 19.2540 mmHg. Pulse, systolic, and diastolic BP pretreatment values were 80.00, 139.9762 mmHg, and 81.7381 mmHg, respectively. The corresponding post-treatment measurements were 79.7143, 140.6429 mmHg, and 82.9524 mmHg which was not significant. The mean IOP reduction was from 11.5961 to 16.2018%.

A one-sample t-test was conducted to compare the mean percentage reduction achieved with twice-daily timolol treatment against the expected minimum percentage reduction of 18%. The analysis showed no statistically significant difference at any of the three time points. The p-values for the 8:00am, 12:00pm, and 4:00pm measurements were 0.220, 0.591, and 0.230, respectively.

Table 6: Intraocular pressure values of twice-daily timolol treatment, 2023 (N=42)

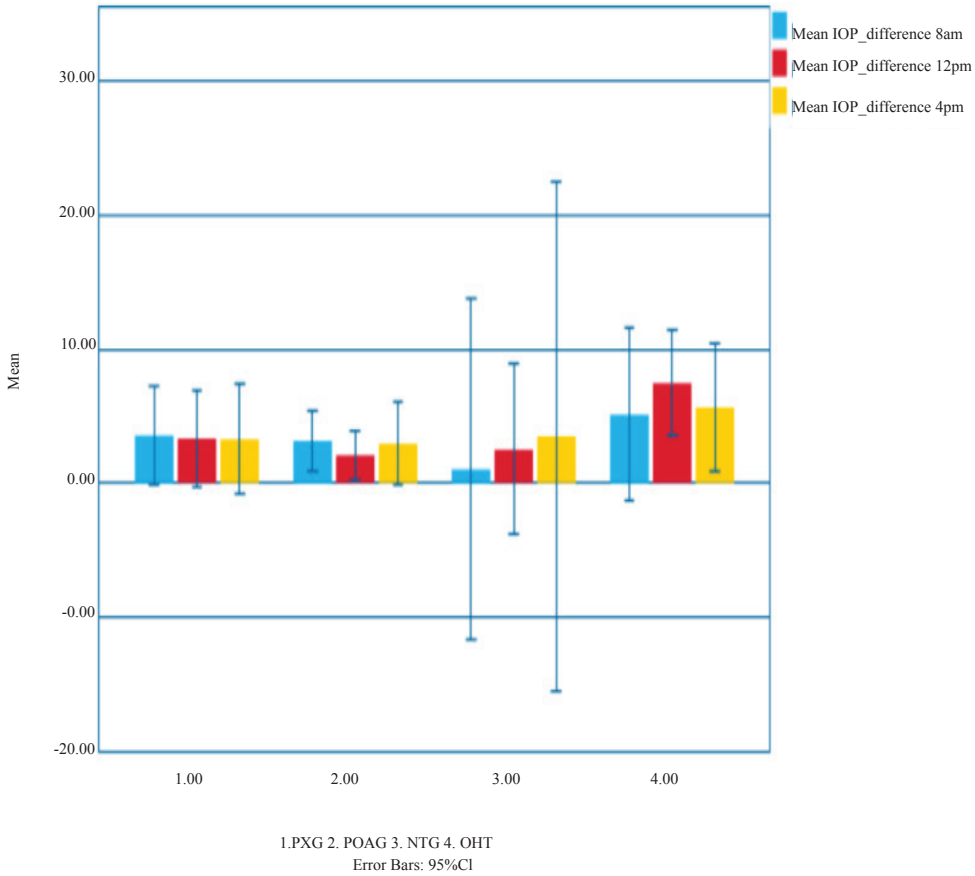
Paired Samples Test[a]

		Paired Differences					t	df	Sig. (2-tailed)
				95% Confidence Interval of the Difference					
Mean		Std. Deviation	Std. Error Mean	Lower	Upper				
Pair 1	Baseline IOP at 8:00am - posttreatment IOP at 8:00am	3.69048	6.60188	1.01869	1.63319	5.74777	3.623	41	.001
Pair 2	Baseline IOP at 12:00pm - posttreatment IOP at 12:00pm	3.95238	5.56536	.85875	2.21809	5.68667	4.602	41	000
Pair 3	Baseline IOP at 4:00pm - posttreatment IOP at 4:00pm	3.78571	6.47899	.99973	1.76672	5.80471	3.787	41	.000

a. 1. twice daily group 2. once daily group = 1.00

The IOP lowering effect of twice daily timolol eye drop treatment on sub-types of OAG or ocular hypertension was higher in ocular hypertension and lower in primary OAG patients & NTG, but this was not statistically significant (Figure 2 and Table 7).

Figure 2: Effect of twice- daily timolol treatment on type of OAG and OHT at the three timings



OAG = Open Angle Glaucoma; OHT= Ocular Hypertension; IOP = Intraocular Pressure; PXG = Psudoexfoliative Glaucoma; POAG = Primary Open Angle Glaucoma, *, †, ‡, §, ||,¶ , **, ††, ‡‡

Table 7: Comparison of mean intraocular pressure reduction at 8:00am, 12:00pm, and 4:00pm among glaucoma subtypes

1. Twice daily 2 Once daily group = 1.00-ANONA-May 16,2026

ANOVA[a]

		Sum of Squares	df	Mean Square	F	Sig.
meanIOP_difference8am	Between Groups	40.619	3	13.540	.295	.829
	Within Groups	1746.357	38	45.957		
	Total	1786.976	41			
meanIOP_difference12pm	Between Groups	194.416	3	64.805	2.290	.094
	Within Groups	1075.489	38	28.302		
	Total	1269.905	41			
meanIOP_difference4pm	Between Groups	52.164	3	17.388	.396	.757
	Within Groups	1668.907	38	43.919		
	Total	1721.071	41			

a. 1. twice daily group 2. once daily group = 1.00

The Wilcoxon signed-rank test showed no statistically significant difference in Pulse Rate (PR), Systolic Blood Pressure (SBP), or Diastolic Blood Pressure (DBP) after treatment, with p-values of 0.705, 0.098, and 0.217, respectively.

Inter-group comparison

There was no statistically significant difference in lowering IOP whether timolol treatment was used once or twice daily. This is shown in Table 8.

Table 8: Comparison of reduction in intraocular pressure between the two groups (N=84)

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
meanIOP_difference8am	Equal variances assumed	.009	.926	.355	82	.724	.50000	1.40958	-2.30410	3.30410
	Equal variances not assumed			.355	81.837	.724	.50000	1.40958	-2.30418	3.30418
meanIOP_difference12pm	Equal variances assumed	.012	.915	-.770	82	.444	-.97619	1.26846	-3.49957	1.54718
	Equal variances not assumed			-.770	81.435	.444	-.97619	1.26846	-3.49983	1.54745
meanIOP_difference4pm	Equal variances assumed	.042	.839	.140	82	.889	.21429	1.52968	-2.82874	3.25731
	Equal variances not assumed			.140	80.295	.889	.21429	1.52968	-2.82971	3.25828

The Mann–Whitney U test showed no statistically significant difference between the once-daily and twice-daily treatment groups in Pulse Rate (PR) and Diastolic Blood Pressure (DBP), with p-values of 0.545 and 0.865, respectively. However, there was a statistically significant difference in Systolic Blood Pressure (SBP) between the two groups (p = 0.045). No significant ocular and systemic adverse effects were reported or observed in either group (Tables 9 – 11).

Table 9: Distribution of reported side effects among the once-daily and twice-daily timolol group

.00		None 1.Ocular irritation 2 .Bluring of vision 3. Allergic conjunctivitis 4. Bradicardia 5. Angina 6. Fatigability 7. Asthmatic attacks 8..Sexual disturbances 9. Depression 10. Fainting episodes 11. Others			Total
		1.00	3.00		
Twice daily group Once daily group	1.00	39	1	2	42
	2.00	40	2	0	42
Total		79	3	2	84

Table 10: Association between timolol dosing frequency and occurrence of side effects using Chi-square test

Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.213a	1	.645		
Continuity Correction	.000	1	1.000		
Likelihood Ratio	.214	1	.644		
Fisher's Exact Test				1.000	.500
Linear-by-Linear Association	.210	1	.647		
N of valid cases	84				

Table 11: Risk estimate of side effects between the once-daily and twice-daily timolol groups

	Risk estimate		
	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for 1. Twice daily group 2. Once daily group (1.00 / 2.00)	.650	.103	4.104
For cohort 1. No 2.Yes = 1.00	.975	.875	1.086
For cohort 1. No 2.Yes = 2.00	1.500	.264	8.523
N of valid cases	84		

Among the 91 patients who completed the one-month treatment period, seven patients were found to be non-adherent based on evaluation using the self-administered adherence checklist. Of these, two patients were from the once-daily treatment group, while five patients were from the twice-daily treatment group. Therefore, only the 84 adherent patients were included in the outcome analysis of the study.

DISCUSSION

In both groups, timolol treatment resulted in a statistically significant reduction in Intraocular Pressure (IOP). Although the observed percentage reduction appeared clinically lower than the expected minimum reduction of 18%, the difference was not statistically significant in either group.

The average reduction in IOP with timolol treatment was not found to be statistically different from the expected reduction (18% to 25%). However, it is essential to note that the mean decrease in IOP observed at three different time points was insignificant but lower than the expected reduction in both regiments. This finding contrasts with the results of other studies, which reported more significant reductions in IOP (meeting or exceeding the expected decrease of IOP)[4 - 12]. Several factors could explain this discrepancy. Firstly, the study's small sample size might have limited its ability to detect significant differences. Additionally, the short duration of the treatment period could have influenced the observed results. The inappropriate application of eye drops or poor adherence to the treatment regimen could also have contributed to the lower reduction in IOP. Moreover, it is worth mentioning that adherence in this study was evaluated based on patient reports, which might not always accurately reflect the accurate adherence level. The other reason could be the poor preparation of the timolol solution drop used for this study. It is essential to consider these limitations when interpreting the findings of this study and to investigate further the potential reasons behind the observed differences in IOP reduction compared to other studies.

This study has compared the effectiveness of timolol in treating different types of OAG and ocular hypertension. The result indicated that there was no specific type of glaucoma or ocular hypertension in which one treatment regimen was more effective than the other. Both regimens were found to lower IOP to a similar extent across all types of OAG and ocular hypertension. Although a slightly more significant reduction was observed in both groups for ocular hypertension and a lesser effect for primary OAG, this difference was not statistically significant. Similar findings were reported in other studies[5,13]. This could be explained by physiological reduction of aqueous humor production at night time. However, it is essential to note that the number of patients, age, and sex were not matched for the sub-types of glaucoma in this analysis. Therefore, further study is recommended to confirm.

There was no statistically significant difference in the systemic effects on Blood Pressure (BP) and Pulse Rate (PR) measurements, and no notable adverse effects were observed when evaluating each treatment group individually. However, comparison between once-daily and twice-daily use of timolol 0.5% solution showed a slight effect on systolic blood pressure in the twice-daily group. Comparative analysis using the Mann–Whitney U test demonstrated marginal statistical significance, with a p-value of 0.045. This marginal effect was not observed in the individual group analyses and may be attributable to the small sample size and short duration of treatment. This finding is consistent with several previous studies[4-12].

There was no statistically significant difference in reducing IOP when 0.5% timolol solution was used once or twice daily during the three time periods that were measured. Similarly, multiple studies have compared the effectiveness of timolol gel formulation administered once daily versus twice daily aqueous timolol solution[4,5-8]. As well as few studies comparing once daily aqueous timolol solution with twice daily timolol aqueous solution have consistently shown similar efficacy in lowering IOP[9,10,12,15]. Some studies comparing the formulation of timolol when used once or twice daily found no statistical difference in lowering IOP[14].

There was no significant difference in ocular or systemic side effects between once-daily and twice-daily use of timolol 0.5% solution. This finding is consistent with results reported in several previous studies[4 – 15].

To minimize the effect of non-adherence on the study outcome, participants' self-administered checklists were reviewed at the end of the one-month treatment period for missed doses. Participants who missed more than 15% of the prescribed doses were replaced by other patients. Accordingly, two patients in the once-daily group and five patients in the twice-daily group were replaced. Therefore, the 84 patients included in the final analysis were considered adherent based on their self-administered checklists. However, this assessment had a limitation, as actual administration of every eye drop dose was not directly observed and adherence relied solely on patient self-report.

Study limitations

This study has limitations. Participant allocation was based on a quasi-randomization method, with the first participant assigned by lottery followed by alternate allocation, which may have introduced selection bias. Baseline differences in age and glaucoma type were present between the groups, and no statistical adjustment for these imbalances was performed. The investigators were not masked. In addition, the one-month follow-up and relatively small sample size may limit the assessment of long-term safety and the generalizability of the findings.

CONCLUSION

The findings of this study suggest that once-daily 0.5% timolol ophthalmic solution may provide intraocular pressure reduction and a safety profile comparable to twice-daily treatment in patients with mild to moderate open-angle glaucoma or ocular hypertension. However, these findings should be interpreted with caution in light of the study limitations.

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