

Pressure lowering effect of fixed combination and unfixed- combination of latanoprost and timolol in Asian population

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Abstract: Introduction: Fixed combination of topical pressure lowering drugs such as latanoprost and timolol (FCLT) has been reported to improve adherence and persistence to medication for chronic disease such as glaucoma. However, its effectiveness has been reported to be less compared to unfixed combination of latanoprost and timolol (UFCLT). Objective: To compare the efficacy of FCLT and UFCLT in Malaysian population. Methods: A non randomized prospective cohort study was conducted from January 2006 to December 2010 involving primary open-angle glaucoma (POAG), ocular hypertension (OHT) and normal-tension glaucoma (NTG) patients who failed to achieve target pressure or demonstrated progression of the disease while on monotherapy treatment with topical timolol XE 0.5% in eye clinic of Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II, Kelantan, Malaysia. A total of 120 glaucoma patients were recruited with 58 were prescribed FCLT and 62 were treated with UFCLT. UFCLT is combination of topical timolol XE 0.5% and latanoprost 0.005%. Intraocular pressure (IOP) was taken at baseline and 3, 6, 9, 12 months post treatment. Results: A total of 95 patients completed the 12 months follow up (47 in FCLT group and 48 in UFCLT). Mean age was 61.0 SD 14.5 years old. Majority of cases were POAG (79%), followed by NTG (12%) and OHT (9%). Mean baseline IOP was 23.9 SD 5.9 mmHg and 19.9 SD 5.6 mmHg in UFCLT and FCLT groups respectively. Mean IOP reduction between baseline and final measurement in UFCLT and FCLT groups were -8.1 mmHg vs.-3.6 mmHg respectively ($p<0.001$). Based on repeated measures analysis of variance (RM ANOVA) and repeated measures analysis of covariance (RM ANCOVA) model, there was significant difference between UFCLT and FCLT ($p=0.002$). Conclusions: Both UFCLT and FCLT provide pressure lowering effect in Malaysian population. UFCLT provides significant better pressure lowering effect than FCLT. FCLT provides less inter-visit pressure fluctuation.

Keywords: Combination Therapy, Latanoprost, Timolol, Ocular Hypertension, Open-Angle Glaucoma, Normal-Tension Glaucoma

1. Introduction

Glaucoma is a group of eye diseases in which there is progressive damage to the optic nerve characterized by specific structural abnormalities of optic nerve head and associated patterns of visual field loss [1]. Elevated intraocular pressure (IOP) is identified as the only modifiable risk factor for the development and progression of glaucoma [2,3]. Topical pressure lowering drugs remain

the most popular, convenient and effective mode of treatment to prevent progression and reduces the risk of glaucoma development [2,3]. However, monotherapy with topical pressure lowering drug is often inadequate to achieve target pressure in most patients. Target pressure is defined as an IOP level below, which further optic nerve damage does not occur [4].

Long term treatment with multiple topical pressure lowering drugs may affect persistency and adherence. It was reported that fewer than 25% of patients were persistent over

12 months of treatment [5]. A combination of more than one drug in a single bottle may potentially improve adherence and persistency in treating chronic disease like glaucoma. Timolol is the most popular, effective aqueous suppressant and has been regarded as 'gold standard' drug for comparison with other drugs for the past 3 decades. The first attempt on fixed combination was timolol and pilocarpine that successfully reduced the frequency of pilocarpine instillation without affecting its effectiveness [6].

Timolol has been combined with various other pressure lowering drugs including prostaglandin analog. Prostaglandin analog is believed to effectively reduce the pressure by enhancing the uveoscleral outflow. It has been proven that adjunctive therapy of latanoprost and timolol provided further pressure reduction as compared to monotherapy of the individual drug [7,8]. Fixed combination of prostaglandin analog and beta blocker is theoretically expected to provide better pressure lowering effect than unfixed combination and fewer unwanted side effect [9,10,11]. In addition, fixed combination of latanoprost and timolol (FCLT) reduces instillation frequency of topical timolol to once daily and simultaneously minimize the exposure to preservatives [12]. On the other hand, timolol in gel forming solution (Timolol XE 0.5%, Merck, USA) also allows once a day instillation without compromising the effectiveness of the drug. Ultimately, although indirectly, FCLT may improve the quality of life of glaucoma patients [13,14].

In spite of the advantages of fixed combination treatment, ineffective pressure lowering effect has also been reported [15]. On contrary, unfixed combination of latanoprost and timolol (UFCLT) was found to provide better pressure lowering effect compared to fixed combination [16]. Most studies referred to UFCLT of timolol in aqueous solution and latanoprost [15, 16]. To the best of our knowledge, there is no available report on the effectiveness of unfixed combination of timolol in gel forming solution and latanoprost. Moreover, there is limited report on the effect of fixed and unfixed combination of latanoprost and timolol in Asian. The aim of our study was to compare the pressure lowering effect of fixed and unfixed combination of latanoprost and timolol in Malaysian population.

2. Methods

A prospective non randomized study was conducted between January 2006 and December 2010 in glaucoma clinic, Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Perempuan Zainab II (HRPZ II); the two main hospitals in Kelantan state of Malaysia. This study received ethical approval from the ethical research board of Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II. Based on slit lamp examination, vertical cup to disc ratio, gonioscopic finding and Humphrey visual field analysis 24-2, diagnosis of primary open angle glaucoma (POAG), ocular hypertension (OHT) and normal tension glaucoma (NTG) were established. Diagnosis of NTG was

based on median IOP of 10 reading ≤ 21 mmHg [17]. OHT was defined based on elevated pressure of >24 mmHg without evidence of glaucomatous damage (18). Inclusion criteria includes inadequate pressure lowering effect with topical timolol XE 0.5% (Timoptol-XE, MSD Inc, USA) monotherapy, failed to achieve the target pressure and evidence of disease progression. Target pressure was predetermined according to the severity of glaucoma, type of glaucoma and baseline intraocular pressure prior to commencement of treatment. Severity of glaucoma was based on Hodapp-Parish-Anderson classification system [19]. For instance, in moderate POAG, the target pressure was set at 15 mm Hg or less and target pressure for moderate NTG was set at 30% reduction from baseline. In cases when bilateral eyes were eligible for recruitment, only the right eye was selected. Any potential participants with a history of intraocular surgery, especially trabeculectomy surgery, were excluded. Systemic comorbidities such as hypertension, diabetes mellitus and hyperlipidemia were also documented.

Baseline IOP was based on the pressure taken using Goldmann Applanation tonometry (GAT) at sitting position between 9am to 12noon prior to the assignment of treatment groups; fixed combination (FCLT) and unfixed combination (UFCLT) of latanoprost and timolol treatment. Topical timolol XE 0.5% gel forming solution (Timoptol-XE, MSD Inc, USA) morning dosing once daily and topical latanoprost 0.005% (Xalatan, Pfizer Inc, USA) night dosing once daily was prescribed for UFCLT treatment. FCLT (Xalacom, Pfizer Inc, USA) was prescribed once daily on morning dosing. There was no 'wash-out' period prior to the commencement of FCLT or UFCLT. The assignment to FCLT or UFCLT was done by glaucoma specialist (LS) and senior ophthalmologist (AY) involving only patients recruited in eye clinic, HUSM. FCLT was not available in HRPZII during the period of this study. Most patients with history of poor adherence to monotherapy treatment with Timolol XE (e.g history of missing follow up appointment and forgetfulness in drug instillation previously) were assigned to FCLT. New target pressure was determined based on the baseline IOP and severity of glaucoma (Hodapp-Parrish-Anderson staging of the latest Humphrey visual field analysis).

Prior the commencement of the drugs, a short briefing was given by a nurse and treating doctor on the important of compliance and proper technique of drug instillation. Double DOT (Do not open and Do occlusion) technique was adopted. At the end of the first visit, the selected patients were prescribed with 1 month supply of either FCLT or UFCLT. Patients were seen again a month later. Subsequent follow up were scheduled at 3, 6, 9 and 12 months. During each visit, IOP was obtained at sitting position between 9am to 12pm. Any recruited patients who failed to achieve target pressure, developed intolerable side effect or shown evidence of disease progression at any point were excluded from the study protocol. Appropriate treatments including additional or switching the pressure lowering drugs and surgical intervention were given to these patients. Patients

who failed to comply with our study protocol were also excluded. For the purpose of analysis only patients who completed 12 months follow up were included.

The available data was then entered into SPSS version 18.0. Double data entry was conducted to minimize missing data and entry error. The comparisons of mean IOP taken at every visit between the two treatment groups were conducted. Repetitive Measure Analysis of Variance (RM ANOVA) was used to analyze the pressure lowering effect between UFCLT and FCLT at baseline, 1, 3, 6, 9 and 12 months. A multiple paired t-test with Bonferroni correction was used to assess the change in mean IOP from baseline in two treatment groups for IOP-lowering medication effect following 12 months of dosing and Pearson chi-square tests were performed to assess statistical difference between the two treatment groups. For the purpose of analysis, the final IOP measurement was set at different level (≤ 21 mmHg, ≤ 18 mmHg, ≤ 16 mmHg and ≤ 14 mmHg). The percentage of patients who achieved the predetermined pressure level was then compared between the treatment groups.

3. Results

A total of 120 patients were recruited based on inclusion and exclusion criteria set at the beginning of the study (58 for FCLT group and 62 for UFCLT). However, only 95 patients (79%) completed the 12 months follow up (47 for FCLT and 48 for UFCLT). 11 patients defaulted follow up, 12 patients required further additional medication and 2 patients were subjected for trabeculectomy surgery. There was no significant difference between the treatment groups and the clinical parameters (table 1).

Table 1. Demographics and clinical characteristics by treatment groups.

Demographic characteristics		FCLT (N=47)	UFCLT (N=48)	p-value
Sex (n,%)	Male	35 (74.5)	28 (58.3)	0.860
	Female	12 (25.5)	20 (41.7)	
Race (n,%)	Malay	39 (83.0)	40 (83.0)	0.617
	Chinese	8 (17.0)	8 (17.0)	
	POAG	36 (76.5)	39 (81.2)	
Diagnosis	NTG	5 (10.6)	6 (12.5)	0.573
	OHT	6 (12.9)	3 (6.3)	
Systemic diseases	HPT	23 (48.9)	10 (20.8)	0.709
	HPL	8 (17.0)	2 (4.2)	0.802
	DM	19 (40.4)	10 (20.8)	0.051
Mean age (SD)		61.7 (14.3)	60.3 (14.7)	0.626*
Mean VCDR		0.7 (0.2)	0.7 (0.2)	0.929*
Mean MD		-13.1 (10.7)	-12.8 (11.1)	0.786*
Mean PSD		6.6 (4.1)	6.6 (3.9)	0.935*

$p < 0.05$, Pearson chi-square test and * student t-test.

POAG-open-angle glaucoma, OHT- ocular hypertension, NTG-normal-tension glaucoma, HPT-hypertension, HPL-hyperlipidemia, DM-diabetes mellitus, VCDR- vertical cup to disc ratio, MD-mean deviation of Humphrey field analysis, PSD-pattern standard deviation of Humphrey field analysis, FCLT- fixed combination of latanoprost and timolol, UFCLT-unfixed combination of latanoprost and timolol.

Table 2. Comparison of mean IOP between FCLT and UFCLT.

IOP	FCLT N=47 Mean(SD)	UFCLT N=48 Mean (SD)	p-value
Baseline	19.9 (5.6)	23.9 (5.8)	0.001
3 months	16.0 (4.1)	15.6 (3.3)	0.585
6 months	16.0 (3.8)	14.7 (3.3)	0.093
9 months	16.4 (2.8)	14.3 (2.9)	0.001
12 months	16.3 (2.8)	15.9 (3.1)	0.531

$P < 0.05$, student t-test.

Mean age of the recruited patients was 60.5 (SD, 14.5) years, with slightly older patients in FCLT treatment group (table1). Majority were diagnosed with POAG. Based on the mean deviation (MD) from Humphrey Field Analysis (HFA), majority were moderate to severe glaucoma. There was slightly higher percentage of diabetes mellitus patients included in the FCLT treatment (table 1).

There was significantly higher baseline IOP in UFCLT compared to FCLT treatment group (table 3 and figure 1).

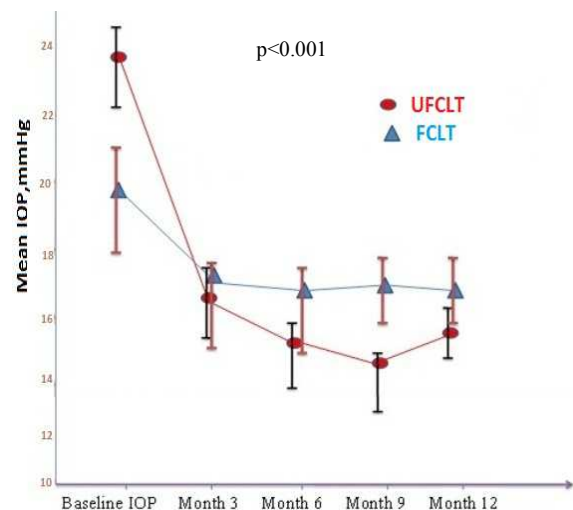


Figure 1. Pressure lowering effect of FCLT and UFCLT for 12 months follow-up based on repeated measure analysis of variance (RM ANOVA).

Both treatment groups showed significant pressure reduction after 3 months treatment. Mean IOP at 9 months post treatment was significantly higher in FCLT group. UFCLT showed statistically significant pressure reduction compared to FCLT. The percentage of reduction of UFCLT was around 40% from the baseline compared to around 20% from baseline in FCLT treatment group (table 3). However, multiple paired t-tests with Bonferroni correction showed that the significant pressure reduction were between the baseline and subsequent follow up for both groups (table 4). There was significant pressure reduction between pressure taken at 9 months and 12 months post treatment with UFCLT (table 4). FCLT demonstrated less inter-visit pressure fluctuation (figure 1). Higher number of patients achieved pressure ≤ 14 mmHg when treated with UFCLT (figure 2).

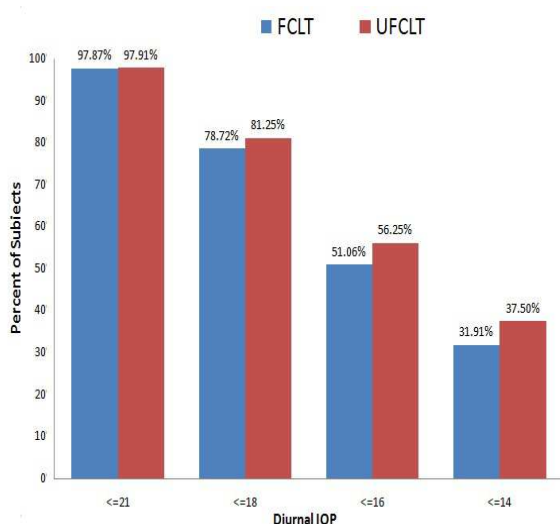


Figure 2. Percentage of subjects who achieved predetermined IOP at 12 months post-treatment..

Table 3. Mean difference and percentage IOP difference from baseline.

Follow-up	Mean IOP difference from baseline (Mean \pm SEM)			Mean % IOP difference from baseline (Mean \pm SD)		
	FCLT	UFCLT	p-value	FCLT	UFCLT	p-value
3 months	-3.9 \pm 0.5	-8.4 \pm 0.5	0.057	20.0 \pm 2.6	34.0 \pm 2.0	0.057
6 months	-3.9 \pm 0.5	-9.2 \pm 0.5	0.050	20.0 \pm 2.6	38.0 \pm 2.1	0.050
9 months	3.5 \pm 0.4	-9.7 \pm 0.4	<0.001	18.0 \pm 2.1	40.0 \pm 1.9	<0.001
12 months	-3.6 \pm 0.4	-8.1 \pm 0.4	0.268	18.0 \pm 1.9	34.0 \pm 1.6	0.268

$P < 0.05$, student *t*-test.

Table 4. Comparison of mean IOP different between follow-up visits according to treatment groups.

Pairing	UFCLT N=48		FCLT N=47	
	Mean IOP different	p-value	Mean IOP different	p-value
Baseline-3 months	8.4(6.5)	<0.001	3.5(3.0)	<0.001
Baseline- 6 months	9.3(6.8)	<0.001	3.5(5.3)	<0.001
Baseline- 9 months	9.7(6.7)	<0.001	3.1(5.4)	<0.001
Baseline- 12 months	88.1(6.4)	<0.001	53.2(4.3)	<0.001
3 3 months- 6 months	10.8(3.5)	0.104	00.0(5.4)	1.000
3 months- 9 months	1.3(3.4)	0.011	-0.4(4.8)	0.606
3 months-12 months	-0.3(3.7)	0.592	-0.3(4.2)	0.650
6 months-9 months	0.5(3.1)	0.313	-0.4(4.0)	0.540
6 months-12 months	-1.1(3.7)	0.038	-0.3(3.8)	0.616
9 months-12 months	-1.6(3.2)	0.001	0.1(3.0)	0.847

$P < 0.005$, multiple paired *t* tests with Bonferroni correction.

4. Discussion

It has been accepted that pressure less than 18mmHg

retard the progression of glaucoma [20, 21]. However, even 1mmHg extra reduction of pressure in advanced glaucoma is clinically meaningful. The Early Management Glaucoma Treatment Study (EMGT) demonstrated that 1mmHg IOP reduction was associated with 10% reduction in visual field progression [22]. Thus, selecting pressure lowering drug that provides maximum pressure lowering and minimum side effects is crucial in the management of glaucoma.

Fixed combination latanoprost and timolol (FCLT) is postulated to increase adherence and persistence, reduced frequency of instillation and perhaps better pressure lowering effect. In our study, the pressure lowering effect of FCLT is not as previously expected. Studies in various populations showed that FCLT was more superior to unfixed combination latanoprost and timolol (UFCLT) [9, 10, 15, 23]. On contrary, our study showed that UFCLT provides almost 2 times more pressure reduction than FCLT. Topical timolol XE 0.5% was more effective prescribed in the morning rather than at night, due to circadian aqueous suppression at night [24]. Latanoprost provides further pressure reduction at night when aqueous production reduces to half. Timolol XE was found to provide slightly better pressure reduction but without significant difference compared to timolol in aqueous solution [25, 26]. Perhaps, combining timolol XE in our UFCLT treatment is partly responsible in better pressure reduction compared to FCLT. However, a short term study on Chinese patients with POAG and OHT, found there was no significant difference between FCLT and UFCLT over 8 weeks open label randomized trial [27]. In this study, once daily timolol morning dosing and once daily night dosing of latanoprost was prescribed. Both FCLT and UFCLT group in Chinese patients achieved almost similar IOP reduction [27].

Similar to study conducted by Zhao et al [27], our study also involved Asian patients. Asians have highly pigmented iris. Pigment is believed to have complex relationship with absorption of topical drugs. Asians and Africans required high concentration of timolol to achieve similar pressure reduction as Caucasians [28, 29]. Caucasians with brown or dark brown irides have higher possibility of discontinuation of timolol treatment due to inadequate pressure lowering effect [28]. The reversible binding of timolol and pigment is believed to be responsible for slow release and cause prolonged sustainable pressure lowering effect [29]. In addition, gel forming solution of timolol is believed to minimize systemic absorption and promotes ocular bioavailability [30,31]. Combination of these factors is perhaps responsible for better pressure reduction in UFCLT treatment in our study. Moreover, latanoprost provides better pressure lowering in Asians and Hispanic patients in multi-populations study [32].

A systematic and meta-analysis involving published papers in Caucasian populations found similar finding; UFCLT provided almost 2 times better pressure lowering effect than FCLT and no difference in mean IOP-lowering effect between evening and morning dosing of a fixed combination of timolol and a prostaglandin F2 α was found [16]. In most studies, only POAG and OHT were

included. NTG was not included due to lower baseline IOP that may cause less pressure lowering effect. On the other hand, higher baseline IOP in UFCLT resulted in more significant IOP reduction.

The magnitude of pressure lowering is not the only important factor in glaucoma management. Fluctuation of IOP plays a role in the progression of glaucoma. It is believed that topical pressure lowering drugs failed to eliminate diurnal fluctuation, which may cause detrimental effect to the nerve fiber layers [33]. However, FCLT treatment in our study shown less inter-visit fluctuation compared to UFCLT treatment. Although the pressure lowering effect was almost 2 times lower in FCLT but in the long term follow up, FCLT provides more stable pressure lowering effect. Perhaps, if the follow up is extended, the UFCLT is expected to provide less pressure lowering effect mainly due to adherence and persistency. Post hoc analysis of EMGT found that inter-visit IOP fluctuation is good predictors for progression [34]. On contrary, AGIS found that the diurnal fluctuation cause detrimental effect in advanced cases [35]. We recruited patients with moderate to severe glaucoma; diurnal fluctuation of pressure is an important issue. However, our study failed to address this matter.

Based on the sample size calculation, our study achieved 80% of calculated sample size. However, comparatively our study is rather small in sample size which could be the source of bias. Absence of randomization could be the source bias, especially those with higher IOP was prescribed UFCLT by chance. Higher baseline IOP is associated with the better pressure reduction [36]. The recruitment of higher number of patients with systemic comorbidities in FCLT group may play a role in less pressure lowering effect or even affect their compliance due to multiple medications for systemic illness. On the other hand, systemic medication especially antihypertensive medication such as beta blockers may affect the pressure lowering effect of timolol. However, when analysis using RM ANCOVA with systemic co-morbidities as co-variants was conducted, UFCLT still provides significant pressure lowering effect.

5. Conclusion

In conclusion, unfixed combination of latanoprost and timolol gel forming solution provided better pressure lowering effect than fixed combination in Asian patients with open angle glaucoma. However, fixed combination provide less inter-visit pressure fluctuation compared to non-fixed combination. Both treatments provide good pressure lowering effect and well tolerated in 12 months follow up.

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