Blind randomised non-crossover long-term trial comparing topical timolol 0.25% with timolol 0.5% in the treatment of simple chronic glaucoma

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SUMMARY The results of a 12-month blind randomised trial comparing the intraocular pressure lowering effect of timolol 0.25% with timolol 0.5% are presented. 27% of patients (22% of eyes) required additional antiglaucoma medication after a minimum time interval of 6 months to maintain an intraocular pressure less than 23 mmHg. The mean reduction in intraocular pressure (from pretreatment values) at 12 months was 24% for eyes treated with timolol 0.25% and 19% for eyes treated with timolol 0.5%. When reductions in intraocular pressure at each follow-up interval were statistically significant (timolol 0.25% treated eyes compared with timolol 0.5% treated eyes), the significance always favoured timolol 0.25%.

Timolol reduces intraocular pressure in both normal and glaucomatous eyes.¹⁻³ It is a non-selective beta-blocking agent, blocking both β -1 and β -2 receptors. In addition it has no intrinsic sympathomimetic or local anaesthetic activity.⁴

Timolol appears to lower intraocular pressure by decreasing aqueous production rather than by increasing aqueous outflow. A reduction in aqueous inflow of 13-48% has been demonstrated by fluorophotometry.⁵

Several short-term studies undertaken to investigate the ocular hypotensive effect of various concentrations of topical timolol have indicated that the lowering of intraocular pressure may be maximal at a concentration of timolol 0.25%.^{3,6,7} In a significant number of patients receiving continuous topical timolol therapy a gradual reduction in the efficacy of timolol (with regard to lowering of intraocular pressure) appears with time (often called 'long-term drift').

This study was undertaken to investigate 2 particular parameters of the therapeutic effect of timolol in open-angle glaucoma. The study attempts to establish the reduction in intraocular pressure which is produced and sustained by the 2 commercially

available concentrations of timolol solution (namely, 0.25% and 0.5%) and whether there is a statistically significant difference between the 2 concentrations, when the reduction in intraocular pressure is compared, after continuous long-term topical instillation. Secondly, this study attempts to provide further information on the incidence and importance of the phenomenon of long-term drift.

Materials and methods

Patients with optic nerve head and visual field changes of open-angle glaucoma, either controlled on topical antiglaucoma medication or presenting as new patients, were considered for the trial. Patients with a history of cardiovascular disease or bronchospasm or who were receiving concomitant medication (any systemic therapy, including diuretics such as acetazolamide) for a cardiovascular disorder were excluded from consideration.

Thirty patients (60 eyes) were included in the trial (14 female, 16 male, mean age 70 years, SD 8.8 years). After a 7-day wash-out period for those patients on topical antiglaucoma medication each patient had a day-curve of intraocular pressures recorded (at 0900, 1200, 1600, and 2000). Intraocular pressures were measured by Goldmann applanation

Table 1 Trial time and intraocular pressure level at which further antiglaucoma medication was instituted

Patient (trial number)	Trial time (months)	Intraocular pressure (mmHg)		Timolol instillation %
		Right	Left	
19	6	24	26	0.25
5	9	30	25	0.25
20	6	30	21*	0.25
4	9	25	25	0.5
18	6	26	28	0.5
30	6	30	24	0.5
21	9	20*	26	0.5
12	12	18*	26	0.5

*Denotes no further treatment required.

Further glaucoma medication given to patients 20, 21, and 12 was gutt. pilocarpin. 2% 4 times daily to the appropriate eye.

and the Haag-Streit slit-lamp. A mean of the day-curve pressures was calculated for each eye and represents the pretreatment intraocular pressure. Each patient was then randomly allocated timolol solution (either 0.25% or 0.5%) to be topically applied twice daily into each eye. All patients were reviewed at one, 3, 6, 9, and 12 months in the clinic by the author. If the intraocular pressure in the same eye was greater than 22 mmHg on 2 successive visits, further antiglaucoma medication was added. Although regular follow-up (in accordance with the trial criteria) was maintained for such patients, subsequent recordings of intraocular pressure were not used in the statistical analysis. Any serious ocular or systemic side effects were noted at each visit.

The code (which was held in the Pharmacy Department) was broken only when all patients had completed a 12-month follow-up.

Results

Of the 15 patients who instilled timolol 0.25% 9 were male, 6 female, and their mean age was 71 years. Of

the 15 who received timolol 0.5% 6 were male, 9 female, and their mean age was 69 years.

In one patient the intraocular pressure rose immediately after timolol 0.25% instillation, which was therefore discontinued. Only 14 continued to instil timolol 0.25%—that is, no replacement was included.

Eight (27%) patients (13 eyes, or 22%) in whom the intraocular pressure was initially controlled following timolol instillation required further antiglaucoma therapy to maintain control (see Table 1). Five were receiving timolol 0.5% and 3 timolol 0.25% (not significant). Seven of these eyes had an intraocular pressure greater than 22 mmHg at both the 3-month and 6-month follow-up periods and additional antiglaucoma medication was begun at 6 months (in accordance with the trial criteria).

The mean pretreatment and follow-up intraocular pressures for eyes treated with timolol 0.25% and timolol 0.5% are shown in Table 2. There is no statistically significant difference (Student *t* test) in the pretreatment mean intraocular pressure values for eyes that received either timolol 0.25% or timolol 0.5% ($0.5 > p > 0.1$). After 12 months of continuous topical timolol instillation the mean reduction in intraocular pressure from pretreatment values is 6.4 mmHg (24%) in eyes receiving timolol 0.25% and 5.0 mmHg (19.4%) in eyes treated with timolol 0.5%. The mean reductions in intraocular pressure from pretreatment values for each follow-up interval are shown in Table 3. Statistical analysis (Student *t* test) of these reductions in intraocular pressure comparing timolol 0.25% with timolol 0.5% instilled into right eyes or left eyes showed little significance. Where statistically significant differences existed they always favoured timolol 0.25% (Table 3).

Side effects were few. One patient complained of occasional hallucinations, and 2 patients complained of tinnitus (likened to egg-shell in the ear) which was temporary.

Table 2 Mean intraocular pressure values at each follow-up period for eyes treated with timolol 0.25% and timolol 0.5%

Time (months)	Mean intraocular pressure ($\pm$ SD) mmHg							
	Right				Left			
	Timolol		Timolol		Timolol		Timolol	
	0.25%	No. eyes	0.5%	No. eyes	0.25%	No. eyes	0.5%	No. eyes
Pretreatment	26.9 ($\pm$ 5.1)	15	24.2 ($\pm$ 3.75)	15	26.8 ($\pm$ 5.5)	15	25.4 ($\pm$ 4.1)	15
1	18.8 ($\pm$ 4.2)	14	19.7 ($\pm$ 2.8)	15	18.9 ($\pm$ 3.2)	14	19.3 ($\pm$ 3.1)	15
3	21.1 ($\pm$ 3.8)	14	18.2 ($\pm$ 3.1)	15	20.6 ($\pm$ 3.8)	14	18.3 ($\pm$ 2.8)	15
6	20.5 ($\pm$ 4.3)	14	20.1 ($\pm$ 4.2)	15	20.1 ($\pm$ 3.2)	14	21.2 ($\pm$ 3.9)	15
9	18.4 ($\pm$ 4.4)	12	17.5 ($\pm$ 3.8)	13	18.6 ($\pm$ 2.9)	13	19.1 ($\pm$ 4.3)	13
12	20.0 ($\pm$ 2.5)	11	19.4 ($\pm$ 2.3)	12	20.8 ($\pm$ 2.1)	12	20.2 ($\pm$ 3.6)	11

The mean intraocular pressure values refer to eyes treated with timolol 0.25% and timolol 0.5% only.

Table 3 Mean reductions in intraocular pressure and significance

Time (months)	Mean reduction in intraocular pressure ($\pm$ SD) mmHg from pretreatment values					
	Right			Left		
	Timolol 0.25%	Timolol 0.5%	p	Timolol 0.25%	Timolol 0.5%	p
Pretreatment	26.9 ($\pm$ 5.1)	24.2 ($\pm$ 3.75)	NS	26.8 ($\pm$ 5.5)	25.4 ($\pm$ 4.1)	NS
1	8.1 ($\pm$ 4.2)	4.5 ($\pm$ 2.8)	0.02 > p > 0.01	7.9 ($\pm$ 3.2)	6.1 ($\pm$ 3.1)	NS
3	5.8 ($\pm$ 3.8)	6.0 ($\pm$ 3.1)	NS	6.2 ($\pm$ 3.8)	7.1 ($\pm$ 2.8)	NS
6	6.4 ($\pm$ 4.3)	4.1 ($\pm$ 4.2)	NS	6.7 ($\pm$ 3.2)	4.2 ($\pm$ 3.9)	0.1 > p > 0.05
9	8.5 ($\pm$ 4.4)	6.7 ($\pm$ 3.8)	NS	8.2 ($\pm$ 2.9)	6.3 ($\pm$ 4.3)	NS
12	6.9 ($\pm$ 2.5)	4.8 ($\pm$ 2.3)	0.05 > p > 0.02	6.0 ($\pm$ 2.1)	5.1 ($\pm$ 3.6)	NS

Statistical analysis (Student's *t* test) has been carried out only on patients treated with timolol only. NS = not significant.

Discussion

A rise in intraocular pressure immediately after the instillation of topical timolol has been previously recorded,^{8,9} but the causative mechanism remains obscure.

In this study 22% of eyes (27% patients) required supportive treatment to reduce the intraocular pressure to normal, but not before 6 months follow-up had elapsed. An incidence of loss of control of intraocular pressure (necessitating additional anti-glaucoma medication) of 19–35% has been recorded.^{3,10,11} This loss of control may represent progressive severity of the disease with ongoing outflow-channel impairment or a reduction in efficacy of timolol with time. Average outflow facility does not appear to change significantly in eyes treated with timolol,^{6,12} though it would be rewarding to look specifically at outflow mechanisms in those eyes which appear to become refractive to timolol with time. The mild reduction in resting pulse-rate following the administration of topical timolol cannot be detected after 6 months' continuous therapy,¹³ again suggesting that tissues may be able to readjust themselves to the presence of timolol. Continuous β -adrenergic stimulation results in a decrease in the number of β -receptors on cell membranes, and conversely adrenergic blockade leads to receptor numbers increasing. Continuous timolol therapy produces an increase in the number of β -receptors in ocular tissues.¹⁴ The exact role that β -adrenergic receptors (without this complicating factor of changes in receptor cell density that occurs during continuous adrenergic stimulation or blockade) play in aqueous humour dynamics remains uncertain.

Although no additional antiglaucoma medication was instituted before 6 months, intraocular pressure levels were raised (i.e., >22 mmHg) in 7 eyes at the 3-month stage (in accordance with the trial criteria). It is important to maintain frequent and regular

follow-up for all patients receiving topical timolol, as a significant number will show a reduction in its effect with time which may continue past the 12-month stage (but was not investigated in this trial).

In those patients (70%) in whom the reduction in intraocular pressure was sustained throughout the trial period there is little clinical significance in the fall of intraocular pressure produced by either timolol 0.25% or timolol 0.5%. Many studies have shown a reduction in intraocular pressure from pretreatment values of 25–30% with a range of 21–46%.^{3,7,15–17} The lack of statistical significance in intraocular pressure reduction when timolol 0.25% is compared with timolol 0.5% has been recorded in previous studies (although not specifically commented upon). Obstbaum *et al.*³ demonstrated a reduction of 7.5 mmHg (29.2% of the pretreatment intraocular pressure) after 3 months of topical timolol 0.25% as compared with a reduction of 7.8 mmHg (27.3% of pretreatment intraocular pressure) with timolol 0.5% over an identical time period. Radius *et al.*⁷ reported a reduction in intraocular pressure of 8 mmHg (26% of pretreatment value) with topical timolol 0.25% as compared with a reduction of 7.0 mmHg (22% of pretreatment value) with timolol 0.5% after one week's therapy. This longer-term study confirms this trend.

Single-dose studies with various concentrations of topical timolol (0.1%, 0.25%, 0.5% and 1.0%) have suggested that a maximum ocular hypotensive effect is achieved with timolol 0.5%.¹⁸ However, if one accepts the fact that the percentage fall in intraocular pressure is a function of the initial intraocular pressure (and in the last study¹⁸ the pretreatment mean intraocular pressures of each treatment group were markedly dissimilar, with the group receiving timolol 0.5% having the highest pretreatment mean intraocular pressure), then the reported results¹⁸ become less meaningful and do not necessarily contradict the results reported here.

The results presented in this paper suggest little difference in effectiveness between long-term topical timolol 0.25% and timolol 0.5%. This suggests that timolol 0.25% should be the initial treatment of choice, and if this proves ineffective (either early or late) then alternative or additive therapy should be considered in preference to the common clinical practice of changing the concentration of timolol to 0.5%. In addition this report confirms the existence and importance of long-term drift (or loss of control with continuous long-term topical timolol).

Timolol continues to have an important role in the medical management of open-angle glaucoma. As further experience with its use accumulates its limitations will become more apparent.

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