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Clinical Trials

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A Double-blind, Randomized Clinical Trial to Evaluate the Efficacy and Safety of Forskolin Eye Drops 1% in the Treatment of Open Angle Glaucoma – A Comparative Study

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Abstract

Objective: We assessed lowering of Intraocular Pressure (IOP) using a herbal formulation, Forskolin eye drops 1% w/v aqueous solution, in the treatment of open angle glaucoma.

Methods: A double blind, randomized, controlled, multi centred trial was chosen as study design to assess the decrease in intraocular pressure with Forskolin 1% w/v aqueous solution eye drops. Ninety patients of either sex, above 18 years of age, suffering from open angle glaucoma with an intra ocular pressure of more than 24 mm/Hg were enrolled in the study. Tonometric readings with no instillation were recorded on baseline visit; the patients were given medication enough to last for the entire study duration and were advised to instill 2 drops thrice a day. The patients were then called for visit 2, i.e. end of 1st week, visit 3-2nd week, visit 4-3rd week, and visit 5-4th week.

Conclusions: The trend towards a decrease in intraocular pressure was higher in the forskolin group for both the eyes as compared to the Timolol group and a reached statistical significance ($p<0.05$). Forskolin 1% w/v aqueous solution was found to be effective and safe in the treatment of open angle glaucoma. Results indicated Forskolin 1% w/v aqueous solution to be more effective than 0.5% Timolol eye drops and thus can be a good alternative treatment of choice in patients with open angle glaucoma.

Keywords: IOP – Intra Ocular Pressure, Timolol, Open angle glaucoma, hypotensive, circadian tonometric pressure.

Introduction

Forskolin, is a labdane diterpene (17-β-acetoxy-8, 13-epoxy-1 α, 6-β, 9 α -trihydroxylabd-14-en-11-one) obtained from the roots of *Coleus forskohlii* an aromatic herb that grows all over India. It was isolated in molecular form of 97% purity. Forskolin has been extensively studied by many researchers for IOP reduction and glaucoma. Despite a lot of research work by many researchers on Forskolin since 1980's, for unknown reasons, none of the companies commercialised it for treating IOP and thereby glaucoma. Sami Labs modified the suspension form of it developed by Hoechst earlier (P.U Witte et al.,) and worked on this molecule extensively in aqueous solution form.

IOP reduction is currently the major therapeutic approach to preserve visual function in patients with glaucoma and the first line of glaucoma treatment [1]. There are many drugs available for lowering IOP acting through various mechanisms either alone or as a combination for the treatment of glaucoma; however, for adequate control of the IOP along with the minimal side effects, new drugs are required. One of the treatments for glaucoma includes beta-blockers and prostaglandin analogues. Beta blockers show systemic side effects that affect the heart and lungs while the increased iris pigmentation with prostaglandin analogues is a disadvantage [2]. Side effects can include, but are not limited to, blurred vision, double vision, drooping eyelid; burning or stinging in eye; headache, weakness, drowsiness; numbness, tingling, or cold feeling in hands or feet; ringing in ears; and dry mouth.

Therefore, a need exists for new ocular hypotensive agents that are more efficacious and have fewer side effects than those used currently. Results from our previous pilot exploratory studies indicate that forskolin eye drops in the aqueous solution form may improve the overall symptoms of glaucoma. Forskolin 1% w/v aqueous solution has been developed from the suspension forms of it developed earlier by Hoechst.

The original ophthalmic formulation using forskolin was made by Hoechst as a suspension in water. They had used an excepient, carboxy methyl cellulose, as an aid to make the suspension in concentrations of 1%, 2% and 4% (percentages refer to the amount of forskolin in the suspension and not the amounts of forskolin in the dissolved state). Sami Labs had the advantage of using a Randomly Methylated Beta Cyclodextrin (RAMEBCD) which allowed us to make clear solution of Forskolin in water up to a concentration of 6% (w/w). Sami Labs first developed a 1% forskolin solution in water using the RAMEBCD and had the clinical trials done and reported to the DCGI. The objective of this study was to evaluate the efficacy and safety of forskolin 1% w/v aqueous solution for the treatment of open angle glaucoma and thereby bring forskolin commercially into the market with no or minimal side effects.

Methods

This study was a double-blind, controlled, comparative, randomized, non crossover trial. The clinical study was approved by

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the Drug Controller General of India, New Delhi and the trial was conducted in accordance with the Good Clinical Practice guidelines and by adhering to all the tenets of the Declaration of Helsinki. Based on our previous study results, a sample size of 90 was calculated and found to be sufficient to give statistically sound results. With respective Institutional Ethics Committee approvals, patients with an intra ocular pressure of more than 24 mm/Hg were enrolled in the study provided these patients had not received miotic therapy within the last 24 hrs and were off systemic therapy for glaucoma for at least 4 days. Patients who met all the Inclusion Criteria but none of the exclusion criteria were selected for the current study: Inclusion Criteria – a) Adult male or female subjects having primary open angle glaucoma, b) Glaucoma with intraocular pressure of more than 24 mm/Hg, c) No miotic or other therapy 24 hours before, d) Off systemic therapy for glaucoma for at least four days, e) Informed consent given. Exclusion Criteria - a) Subjects with conditions like secondary or closed angle glaucoma, bronchial asthma, chronic obstructive pulmonary disease, uncompensated cardiac failure, pregnancy, sinus bradycardia or 2nd or 3rd degree atrio-ventricular block were excluded from the trial, b) Subjects, who have taken any inflammatory ophthalmic dose in the past 3 months, were barred. c) Subjects having concurrent drug intake e.g. β blockers, diamox etc. were also excluded. d) Pregnancy was also exclusion for this trial. No changes were made after trial commencement and the study was done in strict accordance to the Ethics Committee approved protocol.

Ninety adult glaucoma patients were screened and enrolled at three clinical centres across India, with 30 patients per clinical site/center. The nature and purpose of the trial were explained in detail to all participants and their informed consent was obtained, in writing. Allocation of 1% Forskolin and 0.5% Timolol was done in 1:1 ratio between the two groups. At the baseline visit, patients were assessed for demographic and baseline characteristics and also severity of eye symptoms. Patients underwent an intraocular pressure recording by tonometry (HS Climent Clarke International, Model: MK2). The final reading was a mean of 2 readings at 0 hour before medication. Patients were then randomized according to the randomization list into either of the treatment groups. Medication was applied to the eye/eyes presenting with glaucoma. Each eye was analyzed as separate entries and readings were recorded as for right eye and left eye. Patients had regular instillations of the drug throughout the study duration while IOP was measured by the investigators only on the study visits at clinical centres. On the study visits, IOP was measured before and after drug instillations. After application of 2 drops in the eye, tonometric readings were subsequently made at 0.5, 1, 2, 3, 4, 5 and 6 hours.

Patients were free to discontinue or withdraw from the study for the reasons: a) at the request of the patient, b) if the patient was subsequently found to have any listed exclusion criteria, c) if the investigator considers that the patient's health will compromise due to a concomitant illness that developed after entering the study, d) on the emergence of a serious adverse event or an unacceptable laboratory results which in the investigator's opinion necessitates discontinuation of therapy, e) if a patient is recognized after entry to be uncooperative or a consistent violator of protocol requirements (Figure 1).

Sample Size

The sample size was calculated for an alpha error of 0.05 and power at 90%. From our previous studies, we selected the deviation seen in decrease in IOP and on the basis of this data the sample size was calculated to 36 subjects to be able to detect a difference of 1.5 mm Hg. Considering the dropout rate of 20%, a sample size of 45 per arm was considered for the present study. Forty five (45) subjects each were allocated to Forskolin and Timolol groups in 1:1 ratio by using a software (SAS version 9.1), in three different blocks by a biostatistician, for three clinical centers. As this was a double blind study, adequate measures were taken to conceal the identity of Forskolin containers (with both Forskolin and Timolol containers in similar appearance)

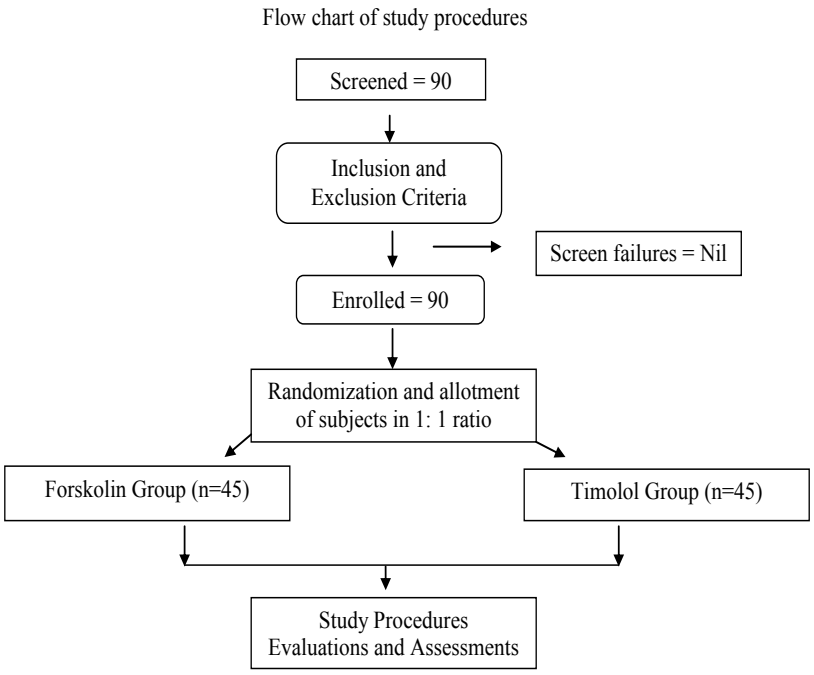

Figure 1: From eligible ninety subjects who were fit into the inclusion and exclusion criteria, 45 were allotted to Forskolin receiving group and 45 to Timolol group. At every follow up visit, study evaluations and assessments were made in both the study groups with no drop outs towards end of the study.

and were supplied to all three clinical centers well ahead of the first patient recruitment. Neither the study investigator (his team) nor the study subjects were aware of the treatment they received and were informed about this blinding as a part of study design. It was only after this explanation a written consent for participation in the trial was obtained from the patients.

Clinical Investigators screened the patients and enrolled them as study subjects as per the pre-determined Inclusion and Exclusion criteria. The patients were called for follow-up visits at the end of 1st week (visit 2), 2nd week (visit 3), 3rd week (visit 4) and 4th week (visit 5) and study procedures were done as per the schedule of events (Table 1). Baseline characteristics are presented in Table 2. The study subjects were given medication as per the randomization sequence and advised to apply 2 drops 3 times a day throughout the study duration of 4 weeks. Patients were advised not to instill the drops on the morning of the follow-up visit. During these visits the signs, symptoms, adverse effect if any and intraocular pressure were recorded in their respective case report forms. Two drops of the medication were instilled at the clinic and the intra ocular pressure was recorded 2 hours after instillation. Same protocol was repeated at all follow-up visits. The primary and secondary outcome measures predetermined in the study protocol as efficacy and safety assessments respectively were evaluated at the end of 4 weeks from baseline visit. No changes were made to trial outcome measures after the trial commenced. Physical and clinical examination, assessment of adverse events and concomitant (intervention) medications were recorded on baseline and all the follow up visits as well. This trial commenced in Feb 2005 and completed in November 2005.

Results

Ninety patients completed the trial. There were no patients lost during follow-up and no drop outs were observed due to adverse effects. Data of all the patients who completed the study was used for statistical analysis.

Vitals (Blood pressure and heart rate) and eye symptoms were assessed for safety assessments. More patients in the forskolin group (13) reported eye symptoms at baseline (pain, corneal edema, blurred vision etc) in comparison to the timolol group (7), however all these were mild in nature and considered as clinically non significant by the study investigators. There were no unintended effects or Adverse Events reported by the study subjects during the regular follow up visits. The subject's well being was enquired during every visit and found no harm to their eye/eyes by the Investigators.

Efficacy assessments

The tonometric recording for each eye at the baseline visit are shown in Table 3 for both the treatment groups. The intraocular pressure was similar in both the groups at baseline. There was a decrease in intraocular pressure in both the groups as shown in Figures 2 and 3 in the final visit (Table 4).

Statistical analysis

Two-way ANOVA test was employed for comparing the results of decreased IOP trend in both the eyes from visit 2 to last visit and between Forskolin and Timolol group patients. Whereas, for the overall decreased trend in IOP between the two groups, simple statistics was employed. The results showed a decreased trend in IOP from visit 2 through last visit between both the treatment groups and the trend towards a decrease in intraocular pressure was higher in the forskolin group for both the eyes as compared to the timolol group; which was statistically significant ($p<0.05$). For descriptive and demographic analysis, simple statistical methods of mean, standard deviation were used.

Discussion

Though a lot of research work has been carried on Forskolin since 1980's, none of the companies commercialized it for treating IOP, for unknown reasons. Few clinical studies on suspension form of Forskolin, though reported its efficacy, had its own limitations. Sami Labs modified the suspension form of Forskolin developed by Hoechst earlier and worked on this molecule extensively in aqueous solution form.

Intraocular pressure (IOP) is normally regulated by changes in the volume of the aqueous humour. Aqueous humor is continually produced by the ciliary processes and this rate of production must be balanced by an equal rate of aqueous humor drainage. Small

Procedures	Screening	Baseline Visit Day 0	Visit 2 Day 7	Visit 3 Day 14	Visit 4 Day 21	Visit 5 Day 28
Signed Informed Consent			X			
Inclusion and Exclusion Criteria			X			
Demographics			X			
Medical History and Physical Examination	X	X	X	X	X	X
Tonometric Readings	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X
Adverse Events	X	X		X	X	X

Table 1: Schedule of Events.

Characteristic	Forskolin eye drops (1%) (n=45)	Timolol eye drops (0.5%) (n==45)
Age (years)	51.1 ± 9.9	52.1 ± 10.4
Male (n)	25 (55.6 %)	29 (64.4 %)
Females (n)	20 (44.4%)	16 (35.5 %)
Weight (kg)	64.0 ± 7.4	62.9 ± 6.6
SBP (mm Hg)	129.1 ± 11.6	131.5 ± 9.2
DBP(mm Hg)	82.4 ± 5.6	81.7 ± 6.2
Heart rate (beats/min)	78.9 ± 6.1	79.2 ± 5.2

Values in percentages and mean ± S.D; n – number of subjects

Table 2: Baseline Characteristics.

	Forskolin eye drops 1%		Timolol eye drops 0.5%	
Intraocular pressure	**Right Eye (mean ± SEM)**	**Left Eye (mean ± SEM)**	**Right Eye (mean ± SEM)**	**Left Eye (mean ± SEM)**
0 hr	29.5 ± 1.13	30.2 ± 0.95	30.0 ± 0.88	29.5 ± 0.80
0.5 hr	27.6 ± 1.03	30 ± 1.09	28.9 ± 0.90	28.8 ± 0.82
1 hr	26.4 ± 0.98	28.5 ± 1.07	27.6 ± 0.91	27.3 ± 0.78
2 hr	25.3 ± 1.04	27.3 ± 1.20	26.8 ± 0.83	26.4 ± 0.75
3 hr	24.6 ± 0.74	27.2 ± 1.07	25.9 ± 0.80	25.7 ± 0.79
4 hr	25.3 ± 1.04	26.6 ± 1.07	26.1 ± 0.82	25.8 ± 0.78
5 hr	26.3 ± 0.86	27.5 ± 0.92	26.5 ± 0.91	26.4 ± 0.84
6 hr	26.4 ± 0.98	27.7 ± 0.86	27.0 ± 0.95	26.9 ± 0.87

Values in percentages and mean ± SEM

Table 3: Intraocular pressure (mm Hg) at baseline visit.

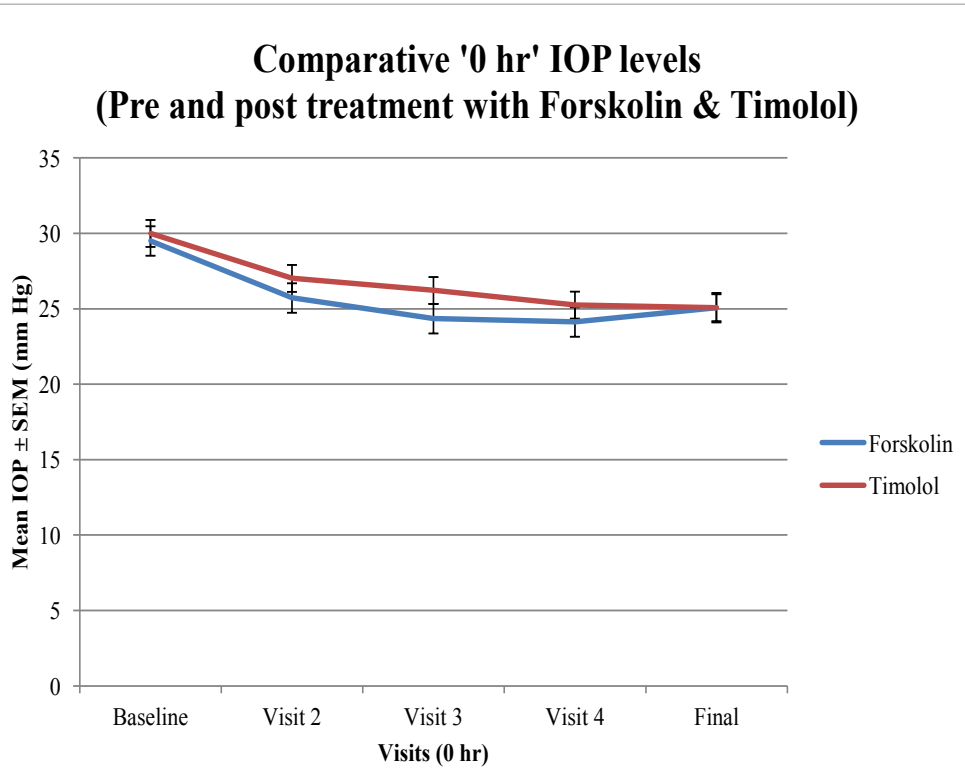

Figure 2: Comparative mean decrease in intraocular pressure between the groups at various visits.

variations in the production or outflow of aqueous humour will have a large influence on the intraocular pressure. The probable mechanism of action of Forskolin is through regulation of aqueous flow by the adenylate cyclase receptor complex in the ciliary epithelium [1-3].

Sear et al., reports the use of Forskolin, a potent noradrenergic stimulator of adenylate cyclase, has allowed a non-invasive study in the human eye of the effects of adenylate cyclase stimulation; i.e., increased cyclic AMP production upon aqueous humor dynamics. The result of decreased intraocular pressure, decreased inflow, and unchanged outflow facility supports the idea that the activated ciliary epithelial adenylate cyclase receptor complex can reduce net aqueous inflow.

P.U Witte et al. at Hoechst, Germany conducted a pilot double blind intra individual comparison of Forskolin eye drops (0.3%-0.6%-1.0% suspension) in 18 healthy male subjects (6 per group) which demonstrated that Forskolin eye drops (0.3%-0.6%-1.0%) lowers intraocular pressure in healthy male subjects. The reduction of intraocular pressure was between 23-28% and the duration of the effect increased with the concentration from 3 to 5 hours.

A randomised, double-blind, placebo--controlled, cross-over design with forskolin eye drops (1.0% suspension) revealed a highly significant maximum reduction of 25% in IOP in 6 hours after instillation of forskolin eye drops [4]. Another study conducted in 1986, concur that two repeated instillations of 1 % forskolin lowered the IOP significantly and decreased the aqueous flow by 13%, while a single instillation had no appreciable effect on the IOP [5]. In males 50 microliter of a topical suspension of 1% forskolin significantly lowered IOP in 1 h, the effect reaching a peak at 2 h, remaining significant for at least 5 hours [6]. In our present study with aqueous solution of 1% Forskolin, we observed the maximum IOP reduction as 21.5%, achieved on day 28. The variation observed was approximately 3.5 % with that of suspension form. Forskolin and its analogues represent a new class of drugs active against glaucoma yet differing in molecular mechanism from that of any previously used drug [7]. The prevalence

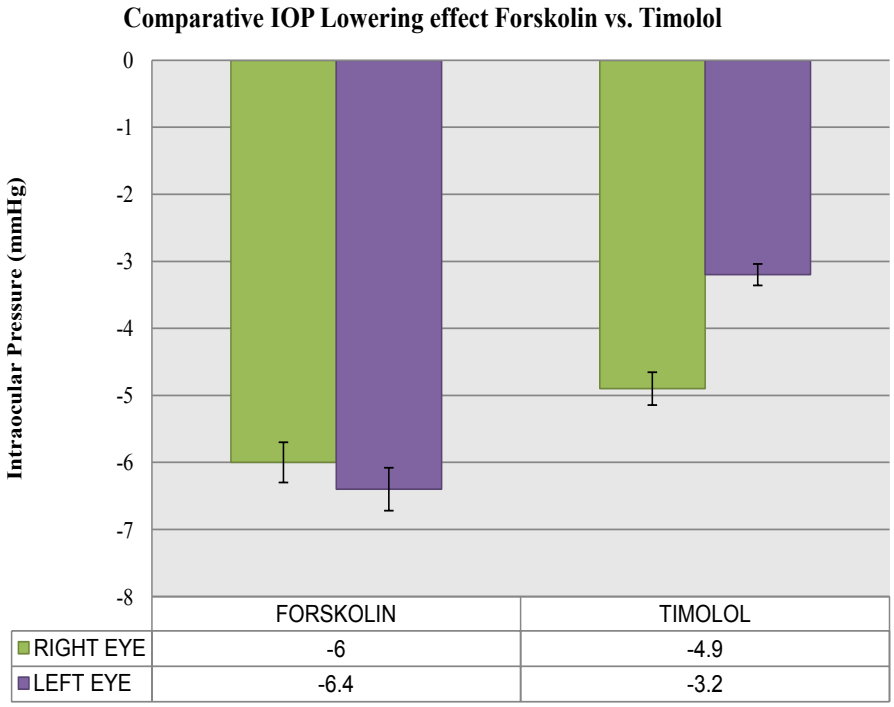

Figure 3: Decrease in IOP levels from baseline to final visit.

Visits		Visit 1 (Baseline)		Visit 2		Visit 3		Visit 4		Visit 5	
Treatment Arm	IOP mm Hg	0 hr	2 hrs	0 hr	2 hrs	0 hr	2 hrs	0 hr	2 hrs	0 hr	2 hrs
Forskolin	Right Eye	29.5 ± 1.13	25.3 ± 1.04	25.72 ± 0.75	23.63 ± 0.72	24.35 ± 0.74	22.72 ± 0.62	24.13 ± 0.74	22.05 ± 0.72	*23.52 ± 0.09	*21.84 ± 0.87
	Left Eye	30.2 ± 0.95	27.3 ± 1.20	26.78 ± 1.12	25.09 ± 0.15	24.80 ± 1.12	23.32 ± 1.03	23.25 ± 0.98	22.17 ± 0.88	*23.71 ± 0.99	*21.93 ± 0.85
Timolol	Right Eye	30.0 ± 0.88	26.8 ± 0.83	27.02 ± 0.95	24.72 ± 0.90	26.22 ± 1.06	24.31 ± 1.01	25.24 ± 1.10	23.64 ± 0.96	25.08 ± 1.06	22.97 ± 1.01
	Left Eye	29.5 ± 0.80	26.4 ± 0.75	26.91 ± 0.89	25.17 ± 0.85	25.84 ± 0.90	23.52 ± 0.93	25.29 ± 0.85	23.38 ± 0.85	25.04 ± 0.83	23.26 ± 0.81

Values in percentages and mean ± SEM; *p<0.05 when compared with their respective visit 5 Timolol group values

Table 4: Effect of treatment on intraocular pressure at every follow up visit.

of complementary and alternative medicine (CAM) use for glaucoma is approximately 5% and forskolin has been used successfully as a topical agent to lower IOP [8].

Vetrugno et al., and Pescosolido et al. studies report a significant effect of an oral food supplement containing forskolin on IOP of patients under maximum tolerated medical therapy. However, in the current study, no oral food supplement containing forskolin was used by patients. In the present study, IOP was measured by a validated Goldmann applanation tonometry [9], as an alternative to the conventional beta blockers and prostaglandin analogues. The enrolled patients were not on any topical medical treatment for their glaucoma. Here, Forskolin 1% eye drops aqueous solution were found to be significantly effective in open angle glaucoma by decreasing the aqueous flow and thereby reduction in IOP. Adverse events were of mild and transient nature.

Conclusion

The results obtained in our trial demonstrate the efficacy of 1% w/v Forskolin (2 drops thrice a day) aqueous solution in achieving fast onset of action and uniformity of hypotensive activity. Forskolin 1% w/v aqueous solution eye drops were significantly ($p<0.05$) effective in lowering the elevated intra ocular pressure in patients with mild open angle glaucoma. It could be an excellent and safe alternative to currently used treatments especially considering its natural origin. The current study on Forskolin 1% aqueous solution eye drops, a formulation developed by Sami Labs Limited, India, confirms the efficacy of the product over a large sample size when compared to Timolol, the widely opted treatment for reduction of IOP in mild open angle glaucoma. Therefore, Forskolin 1% w/v aqueous solution could be recommended as a treatment of choice to Timolol.

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References

1. Aptel F, Chiquet C, Romanet JP (2012) Intraocular pressure-lowering combination therapies with prostaglandin analogues. Drugs 72: 1355-1371.
2. Lindén C, Alm A (1999) Prostaglandin analogues in the treatment of glaucoma. Drugs Aging 14: 387-398.
3. Caprioli J, Sears M, Bausher L, Gregory D, Mead A (1984) Forskolin lowers

intraocular pressure by reducing aqueous inflow. Invest Ophthalmol Vis Sci 25: 268-277.

4. Meyer BH, Stulting AA, Müller FO, Luus HG, Badian M (1987) The effects of forskolin eye drops on intra-ocular pressure. S Afr Med J 71: 570-571.
5. Seto C, Eguchi S, Araie M, Matsumoto S, Takase M (1986) Acute effects of topical forskolin on aqueous humor dynamics in man. Jpn J Ophthalmol 30: 238-244.
6. Caprioli J, Sears M (1983) Forskolin lowers intraocular pressure in rabbits, monkeys, and man. Lancet 1: 958-960.
7. Rhee DJ, Katz LJ, Spaeth GL, Myers JS (2001) Complementary and alternative medicine for glaucoma. Surv Ophthalmol 46: 43-55.
8. Vincent SJ, Vincent RA, Shields D, Lee GA (2012) Comparison of intraocular pressure measurement between rebound, non-contact and Goldmann applanation tonometry in treated glaucoma patients. Clin Experiment Ophthalmol 40: e163-e170.
9. Burstein NL, Sears ML, Mead A (1984) Aqueous flow in human eyes is reduced by forskolin, a potent adenylate cyclase activator. Exp Eye Res 39: 745-749.

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