Saudi Journal of Ophthalmology (2015) 29, 197–200

Original Article

Efficacy and safety of 1% forskolin eye drops in open angle glaucoma – An open label study

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Abstract

Purpose: Current treatment for glaucoma includes beta-blockers and prostaglandin analogues which have their own disadvantages. Thus a need exists for new ocular hypotensive agents that are more efficacious and have fewer side effects. Therefore, forskolin eye drops 1%, through herbal product; a clinical trial was carried out for the safety and efficacy in the treatment of open angle glaucoma.
Methods: Ninety adult male/female patients of 18–60 years of age, of either sex, suffering from open angle glaucoma with an intraocular pressure (IOP) of more than 24 mm Hg were enrolled in the study. Patients were advised to instill 2 drops thrice a day (8:00 h, 14:00 h and 20:00 h) and tonometric readings were recorded on baseline visit and on Visit 2, i.e. end of 1st week, Visit 3–2nd week, Visit 4–3rd week, and Visit 5–4th week. The reduction in IOP across each time point from untreated baseline visit and reduction in IOP across various study visits were measured.
Results: The mean (95% CI) difference in reduction in IOP was 4.5 mm Hg ($P < 0.05$) in the right eye and was 5.4 mm Hg ($p < 0.05$) in the left eye from baseline visit (Visit 1) to final visit (Visit 5).
Conclusions: Forskolin 1% eye drops can be a safe alternative to beta blockers in glaucoma patients having concomitant asthma.

Keywords: Intraocular pressure, Xalatan, Timolol, Open angle glaucoma, Hypotensive

http://dx.doi.org/10.1016/j.sjopt.2015.02.003

Introduction

Glaucoma is a leading cause of blindness and vision loss.[1] It is the most frequent cause of irreversible blindness worldwide and the second most frequent cause of irreversible blindness worldwide after cataract[2] and therefore improved methods of screening and therapy for glaucoma are urgently needed.[3] Persistent high intraocular pressure which characterizes this condition, can lead to worsening of the disease.[4] Currently, there are many drugs available for lowering IOP acting through various mechanisms; however, for adequate control of the IOP along with the minimal side effects, new drugs are the need of the hour.

Coleus forskohlii is an aromatic herb growing all over India from the Himalayas to Southern India. From the roots of this plant is extracted forskolin and it has been studied over the last three decades as a very interesting biological tool.

Current treatment for glaucoma includes beta-blockers and prostaglandin analogues. Beta blockers show systemic side effects that affect the heart and lungs while the

Received 19 May 2014; received in revised form 23 January 2015; accepted 25 February 2015; available online 5 March 2015.

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Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

Production and hosting by Elsevier

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increased iris pigmentation with prostaglandin analogues is a disadvantage.[5] A need exists for new ocular hypotensive agents that are more efficacious and have fewer side effects than those used currently. Results from previous pilot exploratory studies indicate that forskolin eye drops may improve the overall symptoms of glaucoma. The current study on forskolin 1% eye drops, confirms the efficacy of the product over a large sample size, and could be an alternative in asthmatic patients having glaucoma, who are contradicted to use conventional beta blockers.

Materials and methods

The clinical study was approved by the Drug Controller General of India (DCGI), 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. Forskolin 1% eye drops study material was supplied by the manufacturer Sami Labs Limited, India, This trial involved 90 adult patients screened and enrolled at three clinical centers across India. With respective Institutional Ethics Committee approvals, patients diagnosed with open angle glaucoma with an IOP of more than 24 mm/Hg, who had not received miotic therapy for 24 h and systemic therapy for at least 4 days, were enrolled. The nature and purpose of the trial were explained in detail to all participants and their informed consent was obtained, in writing.

Subjects 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 IOP of more than 24 mm Hg, (c) No miotic or other therapy 24 h before, (d) Off systemic therapy for glaucoma for at least four days, (e) Informed consent given. Exclusion Criteria – (a) Subjects with conditions such as 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 anti-inflammatory ophthalmic dose in the past 3 months, were barred. (c) Subjects having concurrent drug intake e.g. β blockers and diamox were also excluded. (d) Pregnancy was also exclusion for this trial. A washout period of 4 weeks has been maintained from the day of screening as per international recommendations.[6]

The enrolled patients were assessed for demographic, complete clinical and physical examination including severity of eye symptoms. Concomitant treatment was also noted (see Table 1). Patients underwent an IOP recording by a validated Goldmann applanation tonometry using a mean of 2 readings at 0 h before study medication was instilled in the affected eye/eyes. Readings were recorded for the right and left eye and both the eyes were analyzed as separate entries. After administering 2 drops of forskolin 1% in the affected eye, tonometric readings were subsequently taken at 0.5, 1, 2, 3, 4, 5 and 6 h. For these IOP measurements, the subjects were to relax 15 min before, and two readings were taken in supine position. These readings were recorded in duplicate, and a mean of two readings was considered for statistical analysis.

The study duration was for 4 weeks. There were 4 follow up visits besides baseline visit (Week 2–Week 5).

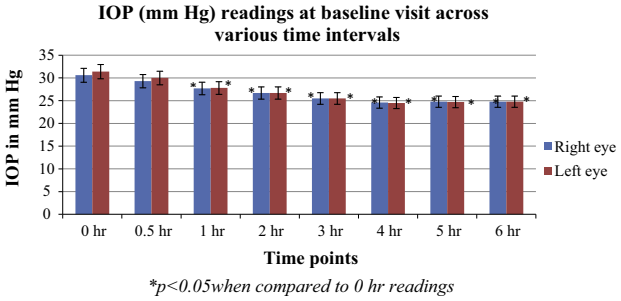

Figure 1. Figures indicate mean decrease in IOP (mm Hg) at baseline visit across various time intervals i.e. 0 h, 0.5 h, 1 h, 2 h, 3 h, 4 h, 5 h and 6 h – postinstillation of forskolin eye drops (1%) [Right & Left Eye]. After administration of first dose (two drops) of forskolin 1% eye drops, decrease in IOP was observed at the first reading (30 min. after administration), reached statistical significance from 1 h onward and IOP continued to drop till 4 h and then remained at plateau for next 2 h.

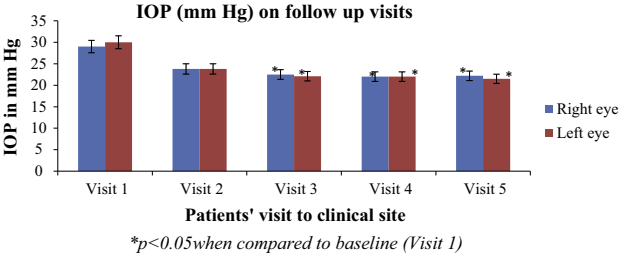

Figure 2. Figure presents effect of treatment on IOP at every follow up visit. It represents the mean decrease in IOP at the first time interval of every follow up visit i.e. Visits 2–5. There was a considerable decrease in the IOP at the first follow-up visit, and reached a statistical significance from second follow up visit (Visit 3) which was maintained till the last study visit.

Throughout the study duration, patients were to instill 2 drops of study medication, 3 times a day (8:00 h, 14:00 h and 20:00 h). Patients were advised not to instill the medication on the morning of the follow up visits, during which, the signs, symptoms and adverse effects were recorded on the Case Record Form. On the day of visit to the clinical site, after administering 2 drops of forskolin 1% in the affected eye, tonometric readings were subsequently taken at 0.5, 1, 2, 3, 4, 5 and 6 h. A qualified personnel who was independent of the study was designated by the Principal Investigator for IOP measurements to avoid potential bias. Tonometric readings were recorded in duplicates and a mean of two readings was considered at the respective time intervals. The same process was followed during all the subsequent visits. Physical and clinical examination, assessment of adverse events and concomitant medications were recorded on all the follow up visits as well. Adverse events were evaluated by asking patients a general query about their state of health since their respective previous or earlier study visits.

Results

Across three clinical centers, ninety subjects (53 males and 37 females) participated in this trial and their mean age was 51.6 ± 11.9 years, and weight 66.0 ± 13.7 kg. Other patient demographic characteristics are depicted in Table 2, as mean

Table 1. Schedule of Events.

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 2. Patient demographic characteristics.

N (sample size)	90
Age (Mean ± S.D.)	51.6 ± 11.9
Male (*n*)	53 (58.9%)
Female (*n*)	37 (41.1%)
Weight (kgs) (Mean ± S.D.)	66.0 ± 13.7
SBP (mm Hg)	128.3 ± 13.5
DBP(mm Hg)	82.7 ± 9.4
Heart rate (beats/min)	78.8 ± 7.0

values. All the 90 subjects enrolled in the trial completed the study and no serious adverse effects were recorded. However, 22 patients reported mild irritation of no clinical significance on instillation, at baseline visit.

Statistical analysis using the SPSS statistical software with the paired t-test at 95% confidence interval (C.I) and 0.05 level of significance showed an effect of forskolin 1% eye drops ($p < 0.05$) on the IOP. Data are present as mean ± SEM, unless otherwise indicated.

Safety

Few subjects reported adverse events such as redness, burning and itching, which were of mild and transient nature lasting for few seconds only and did not lead to withdrawal from the study.

Efficacy

There was a decrease from baseline in the IOP at the first follow-up visit, which was maintained till the end of the study. At a 95% C.I, the mean difference in reduction in IOP, measured in mm Hg, was 4.5 ($p < 0.05$) in the right eye and 5.4 ($p < 0.05$) in the left eye between baseline visit (Visit 1) and final visits (Visit 5) (see Figs. 1 and 2).

Discussion

The estimated prevalence of glaucoma for India is 11.9 million.[7] As of 2010, there were 44.7 million people in the world with open angle glaucoma.[8] IOP is a major risk factor for the development of glaucoma.[9] In open-angle glaucoma, the typical progression from normal vision to complete blindness takes about 25 years to 70 years without treatment, depending on the method of estimation used.[10] The IOP can also have an effect, with higher pressures reducing the time until blindness.[10] There are a range of treatments that have been shown to be effective in slowing down or halting the progress of glaucoma, including the use of medications such as prostaglandins, or surgical techniques, including laser surgery. Increased IOP has long been considered to be the most important risk factor in glaucoma and reduction in IOP has therefore been the treatment of choice in attempting to arrest the propagation of optic neuropathy in patients with glaucoma.[11]

IOP is normally regulated by changes in the volume of the aqueous humor. 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 variations in the production or outflow of aqueous humor will have a large influence on the IOP. The probable mechanism of action of forskolin is through regulation of aqueous flow by the adenylate cyclase receptor complex in the ciliary epithelium.[11]

Sear et al. report the use of forskolin, a potent noradrenergic stimulator of adenylate cyclase, have 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 IOP, decreased inflow, and unchanged outflow facility supports the idea that the activated ciliary epithelial adenylate cyclase receptor complex can reduce net aqueous inflow.

Witte et al. at Hoechst, Germany conducted a pilot double blind intraindividual comparison of forskolin eye drops (0.3%–0.6%–1.0%) in 18 healthy male subjects (6 per group) which demonstrated that forskolin eye drops 0.3%–0.6%–1.0% lower IOP in healthy male subjects. The reduction in IOP was between 23% and 28% and the duration of the effect increased with the concentration from 3 to 5 h.

A randomized, double-blind, placebo–controlled, cross-over design with forskolin eye drops (1.0% suspension) revealed a highly significant maximum reduction in 25% in IOP in 6 h after instillation of forskolin eye drops.[12] Another study conducted in 1986, concurs 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.[13] In man 50 µl 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 h.[14]

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.[15] The prevalence 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.[16]

In the present study, IOP was measured by a validated Goldmann applanation tonometry[17], as an alternative to the

conventional beta blockers and prostaglandin analogues. Here, forskolin 1% eye drops were found to be significantly effective in open angle glaucoma by decreasing the aqueous flow and thereby reduction in IOP.[18] Adverse events were of mild and transient nature. Following this clinical study with 1% w/v, our extensive work on forskolin revealed interesting facts that forskolin is effective in reducing the IOP even at lower strengths i.e., at 0.15%.[19] Therefore, the product was not marketed despite having Indian drug regulatory approval. Currently, randomized, double blind, clinical trial has been initiated in India with forskolin 0.15%.

Conclusion

The results obtained in our trial demonstrate the efficacy of 1% forskolin (2 drops thrice a day) in achieving fast onset of action and uniformity of hypotensive activity. Forskolin 1% eye drops were significantly effective in relieving signs and symptoms of open angle glaucoma. It could be an excellent and safe alternative to currently used treatments especially considering its natural origin. Also its bronchial relaxing effect could be a considerable advantage in asthmatic patients with glaucoma as opposed to beta blockers, which are contraindicated in such patients. Therefore, forskolin 1% could be recommended as a treatment of choice for this condition. Further, confirmatory studies on asthmatic patients having glaucoma are needed on forskolin. Open labelness is the limitation of the present study.

Competing/conflict of interest

The author(s) disclose that financial support for the research described herein was provided by Sami Labs Limited. Dr. Muhammed Majeed is the Founder and Managing Director of Sami Labs and Group of companies; the remaining authors are full time employees of either Sami Labs or its subsidiary Sabinsa Corporation or ClinWorld Private Limited.

Funding sources

Fully funded by Sami Labs Limited, #19/1, 19/2, I Main, II Phase, Peenya Industrial Area, Bangalore 560 058, India

Performed at: M.S. Ramaiah Medical College & Technical Hospital, Bangalore, India; A.G. Eye Hospital, Tiruchirappalli, India; Dr. Agarwal Vasans Eye Hospital, Calicut, India.

Acknowledgments

We thank the Investigators, Dr. Divakar G.V., Dr. Kumararaj G., Dr. Kini S. and other research staff of ClinWorld who were responsible for successful completion of this clinical trial.

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