JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

How to cite this article:
SHARMA R,KOHLI K,KAPOOR B,MENGI RK,SADHOTRA P. THE CARDIO-VASCULAR EFFECTS OF TOPICAL TIMOLOL, LEVOBUNOLOL AND BETAXOLOL IN PATIENTS OF CHRONIC SIMPLE GLAUCOMA.Journal of Clinical and Diagnostic Research [serial online] 2009 June [cited: 2009 August7]; 3:1615-1620.
Available from
http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2009&month= Aug &volume=3&issue=4&page=1615-1620&id=405

ORIGINAL ARTICLE

The Cardio-Vascular Effects Of Topical Timolol, Levobunolol And Betaxolol In Patients Of Chronic Simple Glaucoma

SHARMA R *, KOHLI K* *, KAPOOR B***, MENGI RK****, SADHOTRA P*****.

ABSTRACT

Background: ß–adrenergic antagonists are the most commonly prescribed drugs for glaucoma. However, these drugs can be absorbed into the systemic circulation through the naso-lacrimal duct to produce various systemic side effects.
Aims: The present study was conducted to evaluate the effects of topical timolol, levobunolol and betaxolol on the cardiovascular system in Indian patients of chronic simple glaucoma.
Settings And Design: This prospective randomized single-blind parallel study was conducted in the Department of Pharmacology and Therapeutics in collaboration with the Department of Ophthalmology of a teaching institute.
Methods And Material: Forty newly diagnosed patients of chronic simple glaucoma were included in the study. 16 patients (23 eyes), 12 patients (19 eyes) and 12 patients (20 eyes) were randomized to receive 0.5% timolol maleate, 0.5% levobunolol hydrochloride and 0.5% betaxolol hydrochloride respectively, as one drop twice a day instillation for 12 weeks. Blood pressure, pulse rate and intraocular pressure of each patient were recorded at 0, 6 and 12 weeks.
Statistics: Effects of the individual drug on various study parameters were analysed using the paired t–test. P values <0.05 were taken as significant. A comparative analysis of the effects of the three drugs on the above parameters was done by using the analysis of variance test. Inter-group comparison was done using the Turkey test.
Results: Topical timolol, levobunolol and betaxolol lowered IOP by 13.05 ± 1.53, 14.05 ±1.47 and 7.58 ± 0.90 mm of Hg respectively, at 6 weeks and by 16.12±1.67, 16.28 ±1.85 and 8.53±0.98 respectively, at 12 weeks (P<0.001) .Both topical timolol and levobunolol produced more reduction in IOP than topical betaxolol, with P-values of 0.004 and 0.002 at 6 and 12 weeks respectively. All the three drugs produced a statistically significant reduction in the pulse rate and systolic and diastolic blood pressure, indicating the systemic absorption of ß-blockers in a concentration enough to alter the cardiovascular parameters of the patients .On comparative analysis using analysis of variance, a statistically insignificant difference for change in the three parameters was observed among the three groups .

Conclusion: The results of our study necessitate an urgent need for ophthalmological physicians to exclude all the possible cardiovascular problems in the patients before prescribing a topical ß-blocker.

Key Words: Timolol, levobunolol, betaxolol, blood pressure, cardiovascular, glaucoma.

*(M.D) Senior Demonstrator ,**(M.D.) Associate Professor,***(M.D) Professor and Head, Postgraduate Dept.of Pharmacology and Therapeutics, ****(M.S) Associate Professor ,*****(M.S) Professor and head, Postgraduate Deptt.of Ophthalmology ,Govt. Medical College, Jammu.(India).
Corresponding Address :
Dr Rashmi Sharma, 216-A,
Last-Morh Gandhi- Nagar Jammu, Tawi.
Pin: 180004.J&K state (INDIA)
E.mail:drrashmi@india.com

Intoduction

Drugs whch are topically instilled in the eyes can cause potentially serious systemic effects by their systemic absorption through the nasolacrimal duct. The β–adrenergic antagonists are the most commonly prescribed drugs for glaucoma [1]. The topical administration of timolol, can cause the plasma levels to rise as high as that obtained after intra-venous administration[1].This is because, 50%-70% of the drug escapes first pass metabolism (degradation of drug while passing through intestinal membrane and liver before its absorption into the systemic circulation) [1],[2]. However, betaxolol is a cardio-selective β1–adrenergic antagonist with the theoretical advantage of fewer systemic effects[3],[4] Another drug, levobunolol, a potent non-selective β–adrenergic antagonist, with a longer duration of action (more than 24 hours after single instillation), has been marketed in India [5]. A few studies are available, which demonstrate the effect of topical β–blockers on the cardiovascular system [6],[7]. However, we could not come across any such study on Indian patients. As the variation in the drug's pharmacokinetics and pharmacodynamics with respect to ethnic and genetic variations is a well known fact, we conducted this study to compare the effects of the three topical drugs on the cardiovascular system in Indian patients of chronic simple glaucoma.

Materials And Methods

This study has been described according to the CONSORT guidelines for the presentation of clinical trials. This prospective randomized single-blind parallel study was conducted in the Department of Pharmacology and Therapeutics in collaboration with the Department of Ophthalmology of a teaching institute over a period of six months after taking permission from the institutional ethics committee. It was a time bound study and all the newly registered cases of chronic simple glaucoma (who agreed to enter the study) on two specific OPD (out patient department) days per week, were included in the study.

Inclusion Criteria

A total of fifty newly diagnosed patients with seventy six eyes of chronic simple glaucoma, of both the sexes in the age group of 40 to 80 years, with painless diminution of vision, glaucomatous optic disc damage and glaucomatous field changes, attending the Ophthalmology OPD were initially enrolled for the study. All the patients were subjected to detailed medical and ophthalmic history assessment, complete medical and ocular examination, haematological tests like Hb, BT, CT , TLC , DLC and ESR , biochemical tests like L.F.T., RFT. and blood sugar fasting, urine for routine examination, X-ray chest and E.C.G .

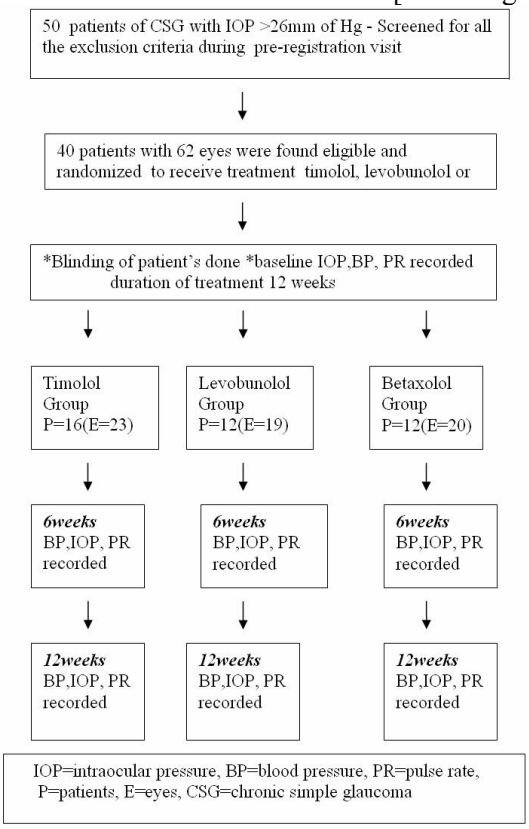
Exclusion Criteria

Patients having one of the following conditions were excluded from the study :- a history of hypersensitivity to timolol ,betaxolol and levobunolol ,ophthalmic surgical procedures within three months of the study, a history of bronchial asthma or chronic obstructive pulmonary disease, cardiac dysfunction including sick sinus syndrome , sinus–bradycardia , 2nd or 3rd degree heart block, congestive heart failure and myocardial

infarction within the past six months ,diabetes mellitus, myasthenia gravis , any systemic malignancy ,liver and renal diseases, psychiatric problems and use of more than one intraocular pressure lowering drugs or any other concommitant drug therapy.

Finally, 40 newly diagnosed patients with sixty two eyes were included in the study after complete screening for the exclusion criteria. The male:female ratio was 11:5, 5:7 and 7:5 in the timolol, levobunolol and betaxolol groups respectively. All patients had baseline (intraocular pressure) IOP>26mmHg. Written informed consent was obtained from all the patients. Fifty opaque envelopes containing random numbers (drugs in code forms), generated with the help of table of randomization, were prepared in advance by an investigator who was not related to the study. Whenever, a study participant was found to be eligible, an envelope was opened by another person in the department and the patient was put on the allocation plan as found inside the envelope in coded form. 23 eyes of 16 patients, 19 eyes of 12 patients and 20 eyes of 12 patients were randomized to receive 0.5% topical timolol maleate (Iotim®-F.D.C. ltd), 0.5% levobunolol hydrochloride (Betagan ® - Allergan) and 0.5% betaxolol hydrochloride (Optipress ® - Cipla) respectively as 1 drop12 hourly instillation [Table/Fig 1] . 0.5% Timolol maleate, 0.5% levobunolol hydrochloride and 0.5% betaxolol hydrochloride were manufactured by FDC Pharmaceuticals Ltd., Allergan Pharmaceuticals and Cipla Pharmaceuticals respectively. All the study drugs were purchased from the market. Drugs in each group were from the same batch. However, the concentration of the drug reaching the systemic circulation has direct influence on the cardiovascular parameters. The selection of 23 eyes in 16 patients, 19 eyes in 12 patients and 20 eyes in 12 patients in the timolol, levobunolol and betaxolol groups respectively, was done due to ethical constraints and hence, study drugs were only instilled in the glaucomatous eyes and not in the healthy eyes of the patients.

Before providing drugs to the patients, the cover labels on the bottles were removed and replaced by paper slips containing the study code. Hence, the patients were not aware about the nature of the drug. All the patients were advised to instill eye drops at 10 o'clock in the morning and in the evening and to maintain a personal diary mentioning the time and date of instillation. Each patient was kept under treatment for 12 weeks and had to undergo three post–registration visits at 0, 6 and 12 weeks. Baseline intraocular pressure (IOP), systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate (PR) of each patient were recorded at '0' week [Table/Fig 2].



(Table/Fig 1) Flow chart showing study design

(Table/Fig 2) Baseline Patient's characteristics

S.no	Timolol (n=16)	Levobunolol (n=12)	Betaxolol (n=12)
*Mean age ± S.D (years)	57.88±16.66	55.91±15.47	61.5±10.83
*Mean weight ±S.D (kg)	67.25±9.60	65.66±11.02	66.3±8.08
*PR/min(mean S.D)	80.62±7.85	77.66±8.30	76.83±7.40
*S.B.P in mm of Hg (mean ±S.D)	136.75±15.64	136.16±13.27	134±10.88
*D.B.P in mm of Hg (mean ±S.D)	79±8.76	78.83±5.42	76±7.28
*IOP in mm of Hg (mean ±S.D)	33.82±9.17	33.45±8.67	30.48±4.052

*Three groups are statistically comparable (p>0.05) significant.

IOP=intraocular pressure, SBP=systolic blood pressure, DBP=diastolic blood pressure, PR=pulse rate, n=number of patients, S.D=standard deviation.

IOP was recorded with the help of an air–puff applantation tonometer on pulse air-200 and a non–contact tonometer (canon T_2). To avoid error in the IOP reading, the mean of three readings was recorded at each visit. Blood pressure was measured on the right arm by the same investigator using a standard mercury sphygmomanometer . Phase 1 and phase V Korotkoff's sounds were used to determine systolic and diastolic blood pressure respectively. Basal blood pressure was measured in the sitting position. Radial pulse at the wrist was felt with the tips of the fingers, with the patient's forearm being pronated and the wrist slightly flexed. The pulse rate was measured by counting the number of beats per minute. IOP, PR, SBP and DBP of all the patients were again recorded at 6 and 12 weeks before instillation of the next dose. Compliance of the patients was confirmed by checking the patient's personal diary. Effects of the drugs on IOP, SBP, DBP and PR were measured as primary variables of the study. However, initially other cardiac complications could not be studied because of the short duration of the study.

Statistics

Effects of the individual drug on IOP, PR, SBP and DBP were analysed using paired t–test. P values <0.05 were taken as significant. 95% Confidence intervals (CI) were calculated according to the standard procedures laid down. Each parameter was expressed as mean ±SD (standard deviation) in tables or as mean ± SEM (standard error of mean) in the results. Comparative analysis of the effects of the three drugs on the above parameters was done by using the analysis of variance test (one way). .Inter-group comparison of the effect on IOP was done by using the Turkey test with a 95% confidence interval. For IOP, each eye was considered as a unit and for PR, DBP and SBP, each patient was considered as a single unit

Results

In the present study, topical timolol, levobunolol and betaxolol lowered IOP by 13.1 ± 1.5(CI= 9.8-16.3) , 14.1 ±1.5 (CI=10.9–17.1) and 7.6 ± 0.9 (CI=5.7-9.5) mm of Hg respectively, at 6 weeks and by 16.1±1.7 (CI=12.6-19.7),16.3 ±1.9(CI =12.4 – 20.2) and 8.5±0.9(CI=6.5-10.6) mm of Hg respectively, at 12 weeks(P<0.001) .Both timolol and levobunolol produced more reduction in IOP than betaxolol [after applying analysis of variance (degree of freedom –drug 2,within groups 59 = total 61) followed by Turkey test], with p-values 0.004 and 0.002 at 6 and 12 weeks respectively .

Topical timolol reduced the mean baseline PR (80.7±1.9 beats/min) by 3.5±0.3 (CI=2.81 – 4.19) and 4.4 ±0.4 (CI=3.60 - 5.14) beats/min at 6 and 12 weeks respectively (P value<0.001). Topical levobunolol reduced the mean baseline PR (77.7 ±2.4 beats/min) by 1.5±0.3 (CI=0.93 – 2.07) (P values<0.001) and 2.3±0.7 (CI= 0.90 - 3.76) beats/min (P values<0.01) at 6 and 12 weeks respectively. Topical betaxolol reduced the mean baseline PR (76.8 ±2.1 beats/min) by 2.2±0.3 (CI=1.59 – 2.73) and 2.5±0.5 (CI=1.5 - 3.5) beats/min at 6 and 12 weeks of the study respectively (P value<0.001).

Topical timolol lowered the baseline SBP (136.8±3.9 mm of Hg) by 3.9±0.3(CI=3.62-5.12) and 3.9±0.4 (CI=3.55 - 5.19) mm of Hg at 6 and 12 weeks respectively (p value<0.001); levobunolol lowered the baseline SBP (136.2 ±3.8 mm of Hg) by 1.2±0.5 (CI=2.50 – 4.16) and 1.7±0.6 (CI=1.90 - 4.42) mm of Hg (p value<0.001) at 6 and 12 weeks respectively ; betaxolol lowered the baseline SBP (134 ± 3.1 mm of Hg) by 3.5±0.7 (CI=2.02 – 4.98) and 5

± 0.9(CI=2.87 – 7.13) mm of Hg at 6 and 12 weeks respectively (p value<0.001).

Topical timolol lowered the baseline DBP (79±2.2 mm of Hg) by 3.9±0.3(CI=3.18 – 4.56) and 3.9±0.4(CI=3.10 - 4.64) mm of Hg at 6 and 12 weeks respectively (p value<0.001), levobunolol lowered the baseline DBP (78.8±1.6mm of Hg) by 1.2±0.5 (CI=0.06 – 2.26) (p value<0.05) and 1.66±0.6 (CI=0.41– 2.91) mm of Hg (p value<0.02) at 6 and 12 weeks respectively and betaxolol lowered the baseline DBP (77.7±2.2 mm of Hg) by 3.5±0.7 (CI=2.98 – 4.68) and 5 ± 0.9(CI=2.02 – 4.30) mm of Hg at 6 and 12 weeks respectively (p value<0.001). On comparative analysis using analysis of variance, it was found that there was no statistically significant difference in the effects produced by the three groups on PR, SBP and DBP, both at 6 and 12 weeks [Table/Fig 3],[Table/Fig 4] . No serious side-effect was reported in any of the groups.

(Table/Fig 3)Mean values of different parameters following treatment with three topical drugs at 6 weeks .

Parameter	Timolol (n=16) Mean ± SD	Levobunolol (n=12) Mean ± SD.	Betaxolol (n=12) Mean ± SD	P-value
1.Pulse Rate (beats/min.)	77.1±6.2	76.2±7.2	74.7±5.7	0.1
2.Systolic Blood Pressure (mm of Hg)	132.4±13.2	132.8±10.8	130.5±10.4	0.1
3.Diastolic Blood Pressure (mm of Hg)	75.1±7.6	77.7±5.0	73.8±7.2	0.1

Non significant difference among three groups after applying one-way ANOVA against dF(degree of freedom) drug-2,within cell-37= total 39.

(Table/Fig 4) Mean values of different parameters following treatment with three topical drugs at 12 weeks.

Parameter	Timolol (n=16) Mean ± SD	Levobunolol (n=12) Mean ± SD	Betaxolol (n=12) Mean ± SD	P-value
1.Pulse Rate (beats/min.)	76.7±7.1	75.3±5.7	74.3±7.6	0.1
2.Systolic Blood Pressure (mm of Hg)	132.4±13.2	133.0±11.5	129.5±9.5	0.1
3.Diastolic Blood Pressure (mm of Hg)	75.1±7.6	77.2±4.3	74.5±6.5	0.1

Non significant difference among three groups after applying one-way ANOVA against dF(degree of freedom) drug-2,within cell-37= total 39.

Discussion

The β–blocker eye drops after topical administration in the eye, may reach the systemic circulation to produce bradycardia and an arterial hypotensive effect [8]. Most of the effects of β–blockers are related to the two known receptor sites →β1- receptors, associated with myocardial contraction and β2-receptors, related to vascular smooth muscles [9].Although bradycardia is a normal response to β-adrenergic blockade, in patients with partial or complete atrio-ventricular conduction defects, β-adrenergic antagonists may cause life threatening bradyarrhythmias [3]. In our study, timolol, levobunolol and betaxolol produced significant reduction in PR, SBP and DBP in agreement with the previous reports [6],[7],[10]. However, a few studies demonstrated a statistically insignificant change in PR, SBP and DBP with timolol ,levobunolol and betaxolol [9],[11],[12]. The insignificant effect on PR, SBP and DBP in these studies may be because of the unsatisfactory wash out period and failure to abolish the preexisting effect of the β–blocker in the patients; as they were already receiving timolol therapy before their inclusion in the study .In 1985, Feghli G J et al also reported that there was no effect of betaxolol on blood pressure(BP) [13].The contradictory results of this study, as compared to the present study, may be because of the use of smaller concentrations (0.25%) of betaxolol; which might have failed to produce enough systemic concentrations to cause any notable change in BP. Moreover, in our study, there was no statistically significant difference in the effects produced by timolol, betaxolol and levobunolol on PR, SBP and DBP, in accordance with the previous reports [7],[9],[12],[14]. Another study by Atkins JM et al demonstrated an insignificant effect on heart rate produced by 1% topical betaxolol single instillation as compared to the placebo during a ten minute treadmill exercise [2]. Whereas, insignificant differences in effects produced by topical timolol and betaxolol on heart rate was reported in the above study, in accordance to our study [2].

However, small sample size and the short duration of the study could be considered as limitations of our study. Moreover, no serious cardiovascular complications were encountered in the three groups by us, as we excluded the patients having the potential for serious adverse reactions due to β–adrenergic blockade from the study. Thus, if there is no evidence of cardiac dysfunction, including sick sinus

syndrome, sinus– bradycardia, 2nd or 3rd degree heart block and congestive heart failure, then any of the topical β–adrenergic blockers could be used [1]. Still, while the patient is under treatment with topical drugs, he should be monitored for a change in BP and PR. However, β-blockers should be used with caution in patients having advanced glaucomatous optic atrophy, as they can further deteriorate the optical disc changes due to ischaemia [8]due to the hypotension brought about by them. Moreover, topical levobunolol, being a longer acting drug, could prove to be a safer alternative as once daily instillation [11]. The gel form of timolol, having the advantages of an efficacy equal to timolol drops, prolonged duration of action, requirement of less frequent administration and poor systemic absorption, could also prove to be a better alternative to topical β-blocker drops [16]. However, further studies are required to rationally establish the quantitative superiority of timolol gel over topical β-blocker drops with respect to systemic absorption and changes in cardiovascular parameters after a long duration of therapy. But one should always take caution while prescribing β-blocking drugs in a glaucoma patient with underlying cardiac abnormality .Moreover, absorption of the drug can be reduced by simple closure of the eye or by applying pressure at the base of the nasolacrimal mucosa [1],[15]. It is vital that the doctor should give proper indications regarding the instillation of the eye drops and screen the patient for all possible contraindications before prescribing β-blocking drugs in a glaucoma patient.

References

[1]. Stephhen CG, Mark J, Alan LR and Gail F S .Clinical pharmacology of Adrenergic drugs. In : The glaucomas, Glaucoma therapy .Ritch R, Bruce M S, Theodore K editors., Mosby- Year Book, Inc. , VOL.111 (second edition) : 1996.p.1425-46.

[2]. Atkins MJ, Pugh RB and Timewell M R .Cardiovascular effects of topical beta-blockers during exercise. Am J Ophthalmol 1985 ; 99(2):173-5.

[3]. Hoffman BB. Adrenoceptor –antagonist drugs. In: Basic and clinical pharmacology. Katzung GB editor. 8th edition (international) Lange Medical Books/ Mc Graw-Hill: 2001:138 -54.

[4]. Collin D. Therapeutic drugs vol. I . Churchill Livingstone. 1999 : B41- 4.

[5]. Collin D. Therapeutic drugs, vol.1I, Churchill Livingstone. 1999 : L29- 39.

[6]. Duzman E, OberM, Scharrer A and Leopold IH. A clinical evaluation of the effects of topically applied levobunolol and timolol on increased IOP. Am J Ophthalmol 1982;94(3):318-27.

[7]. Geyer O, Lazar M, Novack GD, Lue JC and Duzman E. Levobunolol compared with Timolol for the control of elevated IOP. Ann Ophthalmol 1986 oct;18:289-92.

[8]. Hayreh SS, Podhajsky P and Zimmerman MB. Beta-blockers eye drops and nocturnal arterial hypotension. Am J Ophthalmol 1999 ; 128(3):301-9.

[9]. Berry PD Jr., Van Buskirk EM and Shields MB .Betaxolol and Timolol: A comparison of efficacy and side effects. Arch Ophthalmol 1984;102(1):42-5.

[10]. Waldock A, Snape J and Graham CM. Effects of glaucoma medications on the cardio-respiratory and IOP status of newly diagnosed glaucoma patients. Br J Ophthalmol 2000;84(7):710-3.

[11]. Wandel T, Charap AD, Lewis RA, Partamian L, Cobb S, Lue JC, et al. Glaucoma treatment with once daily levobunolol. Am J Ophthalmol 1986; 101 (3):298-304.

[12]. Silverstone D, Zimmerman T, Choplin N, Mundorf T, Rose A, Stoecker J, et al. Evaluation of once daily levobunolol 0.25% and timolol 0.25% therapy for increased IOP. Am J Ophthalmol 1991;112(1) :56-60.

[13]. Feghali JG and Kaufman PL. Decreased IOP in the hypertensive human eye with betaxolol, a beta-1 aderanergic antagonist. Am J Ophthalmol 1985; 100(6):777-82.

[14]. Diggory P, Brown CA , Vail A and Hillman JS. Randomized controlled spirometric changes in elderly people receiving timolol or betaxolol as initial treatment for glaucoma. Br J Ophthalmol 1998;82:146-49.

[15]. Gautam CS, Bhanwra S, Goel NK, Gupta SK and Sood S. Instillation of drugs in the eye. Importance of proper instructions to the patients. Indian J Pharmacol 2001(5);33:386.

[16]. Khamar MB, Bhatt N, Patel K. Serum lipid profile and timolol gel. http.//www.jimaonline.org/oct2002/Drug trial Rep2htm.