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Original Research Article

Timolol Maleate V/s Timolol Maleate with Brimonidine in the Management of Open-Angle Glaucoma Patients with Moderate Intraocular Pressure

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Abstract

Aim: Comparative study between timolol maleate and timolol – brimonidine combination in treatment of open-angle glaucoma of moderate intraocular pressure in a tertiary care hospital

Methods: This observational comparative was carried out in the Department of Pharmacology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. The total number of cases comprises of 100, with 50 in each group. In some patients both their eyes were involved hence I.O.P was measured separately. The concentration of the monotherapy was 0.5% w/v Timolol Maleate. The concentration of the combination therapy was 0.2% w/v Brimonidine Tartrate and 0.5% w/v Timolol Maleate. Both drugs were instilled in the affected eye, twice daily (once in morning and once at night), for a period of four weeks.

Results: There was not much of a significant difference in the gender of the patients, both males and females were affected equally in case of the combination therapy, and the preponderance of female patients (56%) was seen in case of monotherapy of timolol. There was no direct correlation to the presence of comorbidities in the patients. Around 42% was present with both DM (Type 1) and Hypertension in case of monotherapy of timolol. In the case of Timolol-Brimonidine combination, 54% of the patients presented with DM (type 1) and 52% of the patients with Hypertension. This slight increase may be due to the increase in the age of the patients undergoing combination therapy when compared to monotherapy. While 40% of the patients in both the groups had POAG in both their eyes, the remaining patients developed POAG in either the right eye or the left eye. The other eye was only suspected to have glaucoma and the IOP was less than 20mmHg. Hence the sample size to test the efficacy of the drug therapy is a total of 140 eyes, with 70 under each group. Monotherapy of Timolol is seen to lower the IOP at 26% in 3 days, whereas the Timolol-Brimonidine combination therapy lowers the IOP at twice the rate that is 42.86% in 3 days. After reaching a I.O.P of 12mmHg, which is the normal IOP, both the drugs are used for maintenance therapy.

Conclusion: Timolol monotherapy provides the same result as the Timolol-Brimonidine combination therapy and is also comparatively cheaper. Therefore, Timolol monotherapy is better suited for the treatment of POAG in a tertiary care hospital.

Keywords: Timolol, Brimonidine, IOP, glaucoma

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Introduction

Optical hypotensive medication is considered the treat- ment of choice in the initial management of increased intraocular pressure (IOP) in patients with glaucoma.[1,2] Target IOP levels are not always achieved with the use of one agent, however, and many patients require combination therapy. Several new and effective IOP lowering drugs have additive effects when used in combination with the b adrenergic receptor antagonist timolol.[3-6] Latanoprost, the only prostaglandin analogue indicated for first line use as an ocular hypotensive in Europe and the United States, lowers IOP levels by increasing uveoscleral outflow with little or no effect on aqueous humour production, while b blockers are believed to reduce aqueous humour formation.[7-9] The concomitant administration of latanoprost and timolol produces an additive IOP reducing effect.[10,11]Because complex, multidrug regimens can reduce patient compliance, a fixed formulation of latanoprost 0.005% and timolol 0.5% has been made available. Once daily administration of this combination is well tolerated and reduces IOP more effectively than either individual component alone in patients with open angle glaucoma and ocular hypertension.[12-15] Brimonidine, a selective a_2 agonist ocular hypotensive agent, acts by reducing aqueous humour production and increasing uveoscleral outflow.[16]

Compared with timolol in patients with open angle glaucoma or ocular hypertension, brimonidine dosed twice daily produces similar or significantly lower IOP levels when measured 2 hours after a morning dose. Twelve hours after the evening dose (trough), mean decreases in IOP are consistently and significantly greater in timolol treated patients, support- ing the brimonidine labelling recommendation of three times daily dosing.[16] This study compares the effect on IOP of the fixed combination (FC) of latanoprost 0.005% and timolol 0.5% with that of the unfixed combination (UFC) of brimonidine 0.2% and timolol 0.5% in patients with open angle glaucoma or ocular hypertension who previously were uncontrolled on monotherapy or dual therapy. Although the recommended brimonidine dosing regimen is three times daily, twice daily dosing appears to be standard practice

Material and methods

This observational comparative was carried out in the Department of Pharmacology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India.

Patients of Primary Open Angle Glaucoma (POAG) Of age group >=30 years were included in this study.

Methodology

Person has other complications relating to IOP, Person is taking medications other than those described above OR Person is taking additional medication to lower IOP, When I.O.P is higher than normal but person doesn't show signs of glaucoma and Patients with a history of bronchial asthma, COPD and cardiac diseases were excluded from this study.

The total number of cases comprises of 100, with 50 in each group. In some patients both their eyes were involved hence I.O.P was measured separately.

The concentration of the monotherapy was 0.5% w/v Timolol Maleate. The concentration of the combination therapy was 0.2% w/v Brimonidine Tartrate and 0.5% w/v Timolol Maleate. Both drugs were instilled in the affected eye, twice daily (once in morning and once at night), for a period of four weeks.

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The measurement of IOP was done every three days in the morning using Goldmann Applanation Tonometry, which is the gold standard procedure for the measurement of IOP.
Procedure of measurement of IOP by Goldmann Applanation Tonometry

The IOP was measured after the administration of the local anaesthetic drops in order to block the transmission of pain signals, and the fluorescein strips were used to stain the eyes. The beam of the slit on tonometer was adjusted towards the right side of the patient during the IOP measurement of the right eye, while it can be adjusted to the left-hand side of the patient during the IOP measurement of the left eye. Blue and green filters are moved to produce the coloured beam. The beam produced was bright making the fluorescein rings more visible. After fixing the gaze, the patient was asked to look straight with eyes opened widely. By using the thumb, the patient's eyelid must be held gently without applying much pressure on the eye. The blue light from the slit lamp was directed towards the prism ensuring that the head is perpendicular to the eye. The tonometer was slowly moved forward until the prism rests at the centre of the cornea. Using the other hand, the calibrated dial on the tonometer was turned clockwise until the two fluorescein circles in the prism were observed to meet forming a horizontal "S" shape.

The readings on the dial were recorded after withdrawing the prism from the corneal surface. The same procedure was repeated for the other eye after wiping the prism with a disinfectant swab.

Once the IOP was lowered to 12mmHg, the drugs were continued to be instilled twice daily for the remaining duration of the study, as a part of the maintenance therapy.

Statistics
The data collected will be analyzed using Descriptive and Inferential statistics, and the Statistical Software used for Data Analysis is SPSS V22.0 .

Results
Study was conducted on a total of 100 patients of POAG, with 50 patients undergoing monotherapy of Timolol Maleate and the remaining 50 undergoing the combination therapy of Timolol-Brimonidine combination. Demographic details such as the age of the patient, the gender of the patient and association with comorbidities were compared. The age group of the patient was categorized into four categories: Less than 30 years, 30 to 50 years, 50 to 70 years, 70 years and above.

In gender, the patients were categorized into Male and Female. The comorbidities associated that were included are Diabetes Mellitus (type 1) and Hypertension. The efficacy of lowering the IOP in POAG between Timolol Maleate Monotherapy and Timolol-Brimonidine Combination therapy was compared.

The values of IOP were noted every three days from the start of the study (day 0), till day 15, where the IOP had reached 12mmHg. Following this, the IOP was measured once a week, as a part of the maintenance therapy of both the drugs, till the day 28. Adverse effects were rarely seen with both the drug therapies. If seen, they included Dryness of eyes and Redness of eyes, as reported by the patient and examined by the doctor. The adverse effects have been compared.

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Table 1: Comparison between Timolol Maleate and Timolol- Brimonidine combination with respect to the demographic details

Demographic Details	**Timolol Maleate**		**Timolol-Brimonidine Combination**	
Age	No. (n=50)	Percentage.	No. (n=50)	Percentage
Less than 30 years	3	6%	0	0%
35 to 50 years	7	14%	13	26%
50 to 65 years	33	66%	21	42%
65 years and above	7	14%	16	32%
Gender				
Male	22	44%	25	50%
Female	28	56%	25	50%
Comorbidities				
Diabetes Mellitus (Type 1)	21	42%	27	54%
Hypertension	21	42%	26	52%

Table 2: Comparison between Timolol Maleate and Timolol- Brimonidine combination with respect to the efficacy of lowering the I.O.P in POAG

No. of Days	**Timolol Maleate I.O.P Measured**	**Timolol- Brimonidine Combination I.O.P**
	(mmHg) (N=70)	**Measured (mmHg) (N=70)**
0	58	58
3	52	40
6	40	40
9	40	40
12	40	40
15	40	40
21	40	40
28	40	40

Table 3: Comparison between Timolol Maleate and Timolol- Brimonidine combination with respect to the adverse effects (if seen)

Adverse Effects	**Timolol Maleate(N=70)**	**Timolol-Brimonidine Combination(N=70**
Dryness of eyes	3 (4.28%)	3 (4.28%)
Redness of eyes	0 (0%)	3 (4.28%)

Discussion

In India, the estimated number of cases of glaucoma is 12 million, around one-fifth of the global burden of glaucoma

Glaucoma is a group of diseases characterized by a progressive form of optic nerve damage. This is generally, but not necessarily, associated with raised (>21mm Hg) intra ocular pressure (IOP) but the etiology is unknown and there are many risk factors. The chief therapeutic measure is to lower the IOP, either by reducing the secretion of aqueous humor or by promoting its drainage.[5]

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Timolol is the prototype of ocular beta blockers. It is non- selective and has no local anaesthetic or sympathomimetic activity. The ocular hypotensive action (20-35% fall in IOP) becomes evident within 1 hour and lasts for 12 hours.

Brimonidine, on the other hand, is a selective alpha adrenoceptor agonist used as second line add on drug for glaucoma to supplement ocular prostaglandin analogues/beta-blockers. Brimonidine is more alpha 2 selective and more lipophilic. It lowers IOP by 20-27% by reducing aqueous production and by increasing the uveoscleral flow. Peak effect occurs after 2 hours of instillation. Allergic conjunctivitis and other ocular side effects are present.17-21
Timolol monotherapy and Timolol-Brimonidine combination therapy are equally effective in lowering and maintaining the IOP of a patient of POAG. Though Timolol-Brimonidine combination therapy was initially faster in the reduction of IOP, there is no difference in the efficacy of both the therapies, in maintaining the IOP at an optimum of 12mmHg. Hence, the result is the same as that of the monotherapy, with both drugs being equally effective. This result is similar to the various studies conducted across India, where Timolol-Brimonidine combination therapy was faster in lowering the IOP when compared to Timolol monotherapy. However, both the drugs were equally effective in lowering to the optimum IOP and in maintaining it. Both the Timolol Monotherapy and Timolol-Brimonidine combination therapy bring the IOP to a normal level. The IOP was maintained at a constant of 12mmHg as a part of the maintenance therapy for the remaining duration of the study. With respect to the cost, the Timolol monotherapy is priced lower, when compared to Timolol-Brimonidine combination therapy, which is significantly higher.

The study was conducted on a total of 100 patients of POAG, with 50 patients undergoing monotherapy of Timolol Maleate and the remaining 50 undergoing the combination therapy of Timolol-Brimonidine combination.

The comparison of the monotherapy of timolol versus timolol-brimonidine combination therapy with respect to the Demographic details is seen in Table 1.
With the monotherapy of timolol, 66% of the patients belonged to the age group of 50-65 years and only14% of the patients were above 65 years. With Timolol- Brimonidine combination therapy, the patients were significantly older, with 42% of the patients belonging to the age group of 50-65 years and 32% of the patients of the above 65 years.

There was not much of a significant difference in the gender of the patients, both males and females were affected equally in case of the combination therapy, and the preponderance of female patients (56%) was seen in case of monotherapy of timolol.

There was no direct correlation to the presence of comorbidities in the patients. Around 42% was present with both DM (Type 1) and Hypertension in case of monotherapy of timolol. In the case of Timolol-Brimonidine combination, 54% of the patients presented with DM (type 1) and 52% of the patients with Hypertension. This slight increase may be due to the increase in the age of the patients undergoing combination therapy when compared to monotherapy.
While 40% of the patients in both the groups had POAG in both their eyes, the remaining patients developed POAG in either the right eye or the left eye. The other eye was only suspected to have glaucoma and the IOP was less than 20mmHg. Hence the sample size to test the efficacy of the drug therapy is a total of 140 eyes, with 70 under each group. similar study was conducted by some other authors. [22]

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Monotherapy of Timolol is seen to lower the IOP at 26% in 3 days, whereas the Timolol-Brimonidine combination therapy lowers the IOP at twice the rate that is 42.86% in 3 days. After reaching a I.O.P of 12mmHg, which is the normal IOP, both the drugs are used for maintenance therapy. compares the efficacies of both the therapies, up to day 12.
Adverse effects were reported with the usage of both the drug therapies. Dryness of eyes was seen in 4.28% of the patients in both cases. With the Timolol-Brimonidine combination therapy, an additional redness of eyes was seen in 4.28% of patients, which was not reported in case of monotherapy of Timolol.

Conclusion

Timolol monotherapy provides the same result as the Timolol-Brimonidine combination therapy and is also comparatively cheaper. Therefore, Timolol monotherapy is better suited for the treatment of POAG in a tertiary care hospital.

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