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Original Research Article

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

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ABSTRACT

Purpose: To study the efficacy of Timolol Maleate Vs Timolol-Brimonidine combination in lowering the intraocular pressure (IOP) in primary open angle glaucoma (POAG) at a tertiary care hospital. To study any adverse effects of both drug therapies in treatment of POAG.

Methods: Computerized simple randomization was followed in allocating the patients for the two groups. In each group, n=20, is the total number of patients, and N=30, is the total number of eyes tested, since both eyes were involved in some patients. The concentration of the monotherapy was 0.5% w/v Timolol Maleate and concentration of the combination therapy was 0.2% w/v Brimonidine Tartrate and 0.5% w/v Timolol Maleate. Both drugs were administered twice daily and IOP was recorded every 3 days, for a period of 4 weeks.

Results: Monotherapy of Timolol is seen to lower the IOP at 25% in 3 days, whereas the Timolol-Brimonidine combination therapy lowers the IOP at twice the rate that is 50% in 3 days. After reaching a IOP of 12mmHg, which is the normal IOP, both the drugs are used for maintenance therapy. Adverse effects were reported with both groups. Timolol monotherapy is also priced lower, when compared to Timolol-Brimonidine combination therapy.

Conclusion: Timolol monotherapy provides the same result as the Timolol-Brimonidine combination therapy and is also comparatively cheaper. Hence, Timolol monotherapy is better suited for the treatment of POAG.

1. Introduction

In India, the estimated number of cases of glaucoma is 12 million, around one-fifth of the global burden of glaucoma.[1–4]

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]

The collection of glaucomatous diseases is subdivided into open-angle and closed angle glaucoma, both of which can have primary or secondary causes.[6–9]

In the Indian population, an equal proportion of open angle glaucoma and closed angle glaucoma is seen.[1–4]

Open-angle glaucoma is a chronic, progressive and irreversible multifactorial optic neuropathy that is characterized by open angle of the anterior chamber, typical optic nerve head changes, progressive loss of peripheral vision (typical visual field changes) followed by central visual field loss(blindness) for which IOP is an important risk factor.[6–9]

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The IOP rises insidiously and progressively.[5]

Ocular Hypotensive drugs are used on a long-term basis and constitute definitive treatment in a majority of cases.[10]

Topical drugs for glaucoma are beta adrenergic blockers, alpha adrenergic agonists, prostaglandin analogues, carbonic anhydrase inhibitors and miotics.[5]

Topical beta-blockers have been the first line of drugs until recently. They do not affect pupil size, tone of ciliary muscle or outflow facility but lower IOP by reducing aqueous formation. The ocular side effects are mild and infrequent.[5]

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.[5]

Brimonidine, on the other hand, is a selective alpha (2) 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.[5]

The objectives are as follows:

1. To study the efficacy of Timolol Maleate Vs Timolol-Brimonidine combination in lowering the IOP in POAG at a tertiary care hospital.
2. To study any adverse effects of Timolol Maleate & Timolol-Brimonidine combination in treatment of POAG.

This study aims in bringing faster and safer therapy to the disease. This leads to betterment of clinical practices in treatment of POAG.

2. Meterials and Methods

This is an observational comparative study between the efficacy of monotherapy of Timolol Maleate versus Timolol-Brimonidine combination.

The ethical clearance was obtained on 23.12.2019 from the Institutional Ethics Committee (number: RRMCH-IEC/177/2019-20), after which the study was conducted. The study was done in Ophthalmology OPD, Rajarajeswari Medical College and Hospital, Bangalore from January 2020 to January 2021, for a period of one year.

The inclusion and exclusion criteria were strictly adhered to while collecting the patient's data. They are as follows:

2.1. Inclusion criteria

1. Patients of Primary Open Angle Glaucoma (POAG)
2. Of age group >=30 years.

2.2. Exclusion criteria

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

The total number of cases comprises of 40, with 20 in each group. In some patients both their eyes were involved hence I.O.P was measured separately. Therefore, the sample size was increased to 60, with 30 in each group.

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.

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.[4]

2.3. 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.[4]

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.

2.4. Statistics

The data collected will be analyzed using Descriptive and Inferential statistics, and the Statistical Software used for Data Analysis is SPSS V20 and MS Excel. Computerized simple randomization was followed in allocating the patients for the two groups. The study was conducted on a total of 40 patients of POAG, with 20 patients undergoing monotherapy of Timolol Maleate and the remaining 20 undergoing the combination therapy of Timolol-Brimonidine combination. While 50% 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 60 eyes, with 30 under each group.

3. Results

The study was conducted on a total of 40 patients of POAG, with 20 patients undergoing monotherapy of Timolol Maleate and the remaining 20 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 35 years, 35 to 49 years, 50 to 64 years, 65 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.

4. Discussion

The study was conducted on a total of 40 patients of POAG, with 20 patients undergoing monotherapy of Timolol Maleate and the remaining 20 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, 65% of the patients belonged to the age group of 50-64 years and only

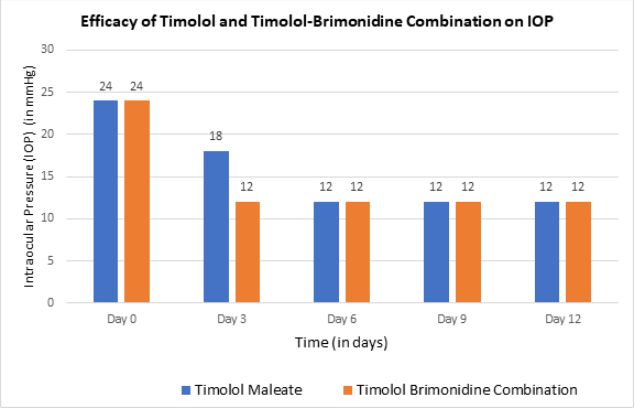

Fig. 1:

15% of the patients were above 65 years. With Timolol-Brimonidine combination therapy, the patients were significantly older, with 40% of the patients belonging to the age group of 50-64 years and 35% 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 (55%) was seen in case of monotherapy of timolol.

There was no direct correlation to the presence of comorbidities in the patients. Around 40% was present with both DM (Type 1) and Hypertension in case of monotherapy of timolol. In the case of Timolol-Brimonidine combination, 55% of the patients presented with DM (type 1) and 50% 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 50% 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 60 eyes, with 30 under each group.

Monotherapy of Timolol is seen to lower the IOP at 25% in 3 days, whereas the Timolol-Brimonidine combination therapy lowers the IOP at twice the rate that is 50% in 3 days. After reaching a I.O.P of 12mmHg, which is the normal IOP, both the drugs are used for maintenance therapy. Figure 1 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 3.3% of the patients in both cases. With the Timolol-Brimonidine combination therapy, an additional redness of eyes was seen in 3.3% of patients, which was not reported in case of monotherapy of Timolol.

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

S. No	Demographic Details	Timolol Maleate		Timolol-Brimonidine Combination	
		No. (n=20)	Percentage.	No. (n=20)	Percentage
1.	**Age**				
	Less than 35 years	1	5%	0	0%
	35 to 49 years	3	15%	5	25%
	50 to 64 years	13	65%	8	40%
	65 years and above	3	15%	7	35%
2.	**Gender**				
	Male	9	45%	10	50%
	Female	11	55%	10	50%
3.	**Comorbidities**				
	Diabetes Mellitus (Type 1)	8	40%	11	55%
	Hypertension	8	40%	10	50%

(NOTE: Here N is the total number of patients under each group)

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

S.No.	No. of Days	Timolol Maleate I.O.P Measured (mmHg) (N=30)	Timolol- Brimonidine Combination I.O.P Measured (mmHg) (N=30)
1.	0	24	24
2.	3	18	12
3.	6	12	12
4.	9	12	12
5.	12	12	12
6.	15	12	12
7.	21	12	12
8.	28	12	12

(NOTE: Here N is the total number of eyes tested in each group)

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

S.No.	Adverse Effects	Timolol Maleate(N=30)	Timolol-Brimonidine Combination(N=30)
1.	Dryness of eyes	1 (3.3%)	1 (3.3%)
2.	Redness of eyes	0 (0%)	1 (3.3%)

(NOTE: Here N is the total number of eyes tested in each group)

5. Conclusion

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. In 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.

6. Abbreviations

IOP: Intraocular pressure; POAG: Primary open angle glaucoma.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Quigley HA. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262–7. doi:10.1136/bjo.2005.081224.
2. Ocansey S, Abu EK, Abraham CH, Owusu-Ansah A, Acheampong C, Mensah F. Socio-demographic factors modify awareness, knowledge, and perceived risk of glaucoma in rural and urban residents in Ghana: a population-based survey. *Ther Adv Ophthalmol*. 2021;13. doi:10.1177/2515841421998099.
3. Chandrashekharan S, Rengappa R, Gunaselvi R, Maheshwari D, Kader MA, Chakrabarty S. Agreement of findings of glaucoma screening between trained vision center technicians and glaucoma specialists at a tertiary hospital in South India. *Indian J Ophthalmol*. 2021;69(4):871–5. doi:10.4103/ijo.ijo_1390_20.
4. Hu D, Jiang J, Lin Z, Zhang C, Moonasar N, Qian S. Identification of key genes and pathways in scleral extracellular matrix remodeling in glaucoma: Potential therapeutic agents discovered using bioinformatics analysis. *Int J Med Sci*. 2021;18(7):1554–65. doi:10.7150/ijms.52846.
5. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. Replika Press; 2019.
6. Mahabadi N, Foris LA, Tripathy K. Open Angle Glaucoma. Treasure Island (FL): StatPearls Publishing; 2021.
7. Padala S, Sripada R, Gundabattula SBP, Tadi KJ, Nallamothula PR, Raveshi F, et al. A comparative study on the efficacy of brinzolamide/timolol versus brinzolamide/brimonidine fixed drug combinations in primary open-angle glaucoma. *Future J Pharm Sci*. 2020;6(1):38. doi:10.1186/s43094-020-00058-6.
8. Weinreb R, Aung T, Medeiros FA. The Pathophysiology and Treatment of Glaucoma. *JAMA*. 2014;311(18):1901–11. doi:10.1001/jama.2014.3192.
9. Malihi M, Filho ERM, Hodge DO, Sit AJ. Long-Term Trends in Glaucoma-Related Blindness in Olmsted County, Minnesota. *Ophthalmology*. 2014;121(1):134–41. doi:10.1016/j.ophtha.2013.09.003.
10. Harasymowycz P, Birt C, Gooi P, Heckler L, Hutnik C, Jinapriya D. Medical Management of Glaucoma in the 21st Century from a Canadian Perspective. *J Ophthalmol*. 2016;2016:1–22. doi:10.1155/2016/6509809.

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