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Original Article

Pharmacology Section

Cost Analysis of Commonly used Combination of Drugs in Primary Open Angle Glaucoma

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ABSTRACT

Background: Glaucoma is second cause of blindness in the world. The financial burden on the patient during long-term treatment is immense and affects the compliance to medications, thus visual morbidity.

Objective: To analyse economic impact of three commonly used drug combinations (Dorzolamide+Timolol=DT; Brimonidine+Timolol=BT; Latanoprost+Timolol=LT) in primary open angle glaucoma.

Materials and Methods: This observational, prospective study was undertaken at M & J Institute of Ophthalmology, Civil Hospital, Ahmedabad, a western regional institute of Ophthalmology. A total of 257 patients were included in the study. Only101 patients could complete the 6 month follow-up, of which 35, 34 and 32 patients belonged to DT, BT and LT group respectively. Cost of drug, details of the transportation were noted at every visit. Total cost incurred per patient/eye was calculated. Cost effectiveness was calculated by cost per mm Hg IOP (Intra-Ocular Pressure) reduction.

Results: Treatment with DT, BT & LT group consumed 8.6%, 4.6% and 7.7% of the per annum income of the family, respectively. Cost of medications per annum (in INR)/eye for DT, BT & LT group were 2562 ± 15.74, 1544 ± 32.06, 3876 ± 73.68 (Mean±SEM) respectively. Additional cost of travelling was different for patients coming from Ahmedabad (Locals) and outsiders (patients coming outside Ahmedabad, India). Outsiders has to bear the brunt of higher transport charges, where they spent an average of Rs. 914, 856 & 933 per annum (5 follow-ups), whereas, Locals spent an average of Rs. 104, 112, 100 for DT, BT & LT group respectively.

Conclusion: Treatment with BT was found to be most cost-effective among three groups. Drug therapy takes substantial amount from per annum income of family and was an important compliance factor in the treatment of POAG.

Keywords: Cost-effectiveness, Drug Combinations, Economics, Intra-ocular Pressure

INTRODUCTION

Glaucoma is second leading cause of blindness in the world with primary open angle glaucoma (POAG) being common subtype [1]. Among different subtypes, POAG is challenging, right from diagnosis to treatment, because of its chronic, insidious onset and slow progression over the years. By the time patient presents clinically with only perceivable symptoms of visual field defects, it has been observed, that one third or more of the optic nerve fibres will be damaged and approximately 90% or more of axons are lost [2]. This compels physician to emphasize on the importance of taking medications to the patient, at the earliest possible time, single or multiple drugs, throughout life [3]. This life time treatment poses a financial challenge to the patient and adversely affects the drug compliance, which is, as in any chronic diseases, plays a major role in treatment outcome. Though compliance depends on age, sex, level of education, severity of the disease, and fear of blindness but cost of medication/s plays an important role in influencing drug compliance [4], especially in developing country like India.

Treatment of POAG typically starts with single agent like timolol or latanoprost but eventually like most (75%) of the patients in Collaborative Initial Glaucoma Treatment Study (CIGTS) required to use two or more drugs to achieve target intra-ocular pressure (IOP) [5], end up in dual or triple poly-pharmacy. Therefore we studied three different drug combinations namely Dorzolamide plus Timolol (DT), Brimonidine plus Timolol (BT) and Latanoprost plus Timolol (LT), which are commonly prescribed in our setup, in the treatment of POAG. These additional medications add to the cost of treatment, which seriously affects the compliance, especially in rural and middle-class of India, where money takes priority over health & disease. Therefore, it is important to use the combination of drugs which are cost-effective, so as to improve compliance and thus quality of life [6] of patient with POAG. The present study is aimed at cost-analysis of the three commonly used drug combinations used in a tertiary level health care centre.

MATERIALS AND METHODS

It was continuous, prospective, longitudinal and observational study conducted over a period of 18 months, at M. & J. Institute of Ophthalmology, Civil Hospital, Ahmedabad, Gujarat. Institutional Ethics Committee approval to conduct the study was taken before commencing the study. The investigator attended the OPD of Glaucoma Unit at above institute on every Tuesday and Saturday. Investigator took informed consent from the patient (both sex and >40 years) and recorded data regarding the drugs prescribed, cost of the drugs, monthly or annual income, residential address, family size, travel expenses (only patient's) etc. in a systematic Case Record Form (CRF), after a patient being diagnosed as case of POAG and was prescribed one of the three combinations of drugs, namely, Dorzolamide plus Timolol (DT), Brimonidine plus Timolol (BT) and Latanoprost plus Timolol (LT) by the ophthalmologist. The follow up of the each patient was done at an interval of 1 month, 3 months, and 6 months. At every subsequent visit, similar enquiries as above were done. Data was analysed at the end of the study by ANOVA for inter-group analysis & t-test for intra-group analysis.

Only those patients who have completed the 6 months follow-up with compliance to the treatment were included in the study. Compliance was ensured by enquiring patients and/or patient-attender by asking direct and indirect questions on drug use. Patients, who refused consent, change of medications during 6 months follow-up, goes for surgical treatment of POAG, who have less than 6 months follow-up, concomitant ocular diseases which

are likely to affect glaucoma treatment-related costs & patients who were not compliant were excluded.

Costs incurred annually (direct & indirect) were measured in Indian National Rupees (INR). Conversion of INR to USD, wherever necessary, are done at the exchange rate of 1 USD= INR 62. The cost of the drug was noted from the label of the preparation. The costs of drugs were based on estimates in April, 2014. In our study we assessed costs for only one diseased eye per patient. Mean cost of drugs per eye per year was extrapolated from analysis of 6 months treatment, assuming no follow-up visit to the hospital until 12 months {Eye drops- 1 ml= 25 drops at mean size of the drop being 40 microlitre [7-9] were calculated by cost per milli-litre of the drugs}.

The cost incurred due to travelling was calculated by using the fare structure given in Gujarat State Road Transport Corporation website http://www.gsrtc.in/GSRTCOnline/ for patients travelling from places beyond the area of operation of Ahmedabad, India Municipal Transport Services (AMTS) (Outsiders). The cost of travelling for patients, who were within the area of operation of AMTS (Locals), was calculated using AMTS fare structure from http://www.amts.co.in/SitePage.aspx?id=35. The fare was estimated using fare structure of April 2014. An additional follow-up at 12 months (Follow-ups: at 0, 1, 3, 6 and 12 months) was assumed and transport charges added to final cost accordingly.

RESULTS

This observational study was undertaken at M & J Institute of Ophthalmology, Civil Hospital, Ahmedabad, and a western regional institute of Ophthalmology to study "Pharmaco-economic analysis of primary open angle glaucoma with three commonly used combinations of drugs". The results are tabulated as below:

The baseline characters shown below were noted and found to be not significant statistically before commencing the study [Table/Fig-1].

Characteristics	DT Group (n=35)	BT group (n=34)	LT group (n=32)
Age (in years)*	46±11.1##	49.29±12##	48.47±11.9##
Gender (M:F ratio)	1.46	1.42	1.05
Per annum Income of the family*	125246 ± 12473#	127765 ± 10270#	204000 ± 28445#
Per capita Income*	29659 ± 3294#	33559 ± 3019#	50563 ± 7021#
Baseline IOP in mmHg*	25.7±4.2##	26.3±5.86##	26.5±4.76##

[Table/Fig-1]: Baseline characteristics.
*p>0.1 (ANOVA test),# Mean±SEM, ##Mean±SD

Economic Status

Most of the patients in DT group (23) belonged to low income group followed by 12 patients in BT group, whereas none of the patients belonging to low income group was prescribed LT combination. In LT group, 11 out of 32 patients were in to high income group [Table/Fig-2].

Per Annum income (in INR)	DT group (n=35)	BT group (n=34)	LT group (n=32)	Total
Less than 40,000	23	12	0	35 (34.65%)
40,001 to 80,000	8	4	5	17 (16.83%)
80,001 to 1,20,000	3	14	9	26 (25.74%)
1,20,001 to 1,60,000	0	3	7	10 (9.9%)
More than 1,60,000	1	1	11	13 (12.87%)

[Table/Fig-2]: Distribution of economic status

Cost of the Treatment

We calculated cost of the treatment for only one affected eye. It was then extrapolated to find cost incurred when both eyes are involved. The expenditure incurred is given in [Table/Fig-3].

	DT (n=35)	BT (n=34)	LT (n=32)
Per annum income of the family (in INR)#	125246±12473	127765 ± 10270	204000 ± 28445
Per capita Income (in INR)#	29659 ± 3294	33559 ± 3019	50563 ± 7021
Cost of drug/Year/Eye (in INR)#	2562 ± 15.74	1544 ± 32.06	3876 ± 73.68
Cost of drug/Year/Both Eyes (in INR)#	5124 ± 32.36	3,088 ± 64.13	7752 ± 152
Cost of travel (5 follow-ups) by Locals (in INR)*	104	112	100
Cost of travel (5 follow-ups) by Outsiders (in INR)*	914	856	933
Total cost of treatment/year/Eye -by Locals (in INR)*	2666	1656	3976
Total cost of treatment/year/Eye -by Outsiders (in INR)*	3476	2400	4809
% of Per capita/annum Income#	8.6	4.6	7.7

[Table/Fig-3]: Cost of Glaucoma treatment
#Mean±SEM; * Mean

It is evident from the table that the treatment with BT is cheaper followed by DT and LT combination being most expensive, more than double the cost incurred by BT group. Patients of three groups, DT, BT & LT spent 8.6%, 4.6% and 7.7% of their per annum income of the family.

Transport Costs

Since study population included both locals and outsiders, naturally outsiders spent [Table/Fig-3] more money which actually escalated the costs. While calculating the outsider's cost, we also added addition bus-fare to & from Ahmedabad central bus stand to civil hospital, Asarwa, Ahmedabad, India.

Cost of per mm Hg IOP

Cost incurred by the patient per mm Hg of IOP reduction was calculated for a period of six months of study period. Cost per mm of Hg reduction is calculated as,

Cost per mm of Hg reduction = Mean total cost of treatment per year ÷ Mean change from baseline IOP (mm Hg).

Group	Baseline IOP (mm Hg)	IOP after 6 months	Mean change in IOP	Cost /mm Hg Reduction (in INR)
DT (n=35)	25.7±4.2	17.85±3.16	7.83*	164
BT (n=34)	26.3±5.86	17.9±4.4	9.38*	82
LT (n=32)	26.5±4.76	16.8±4.11	9.64*	207

[Table/Fig-4]: Cost effectiveness at 6 month
*p<0.05 (Intra-group change in IOP)

The IOP reduction was statistically significant with each combination (Intra-group) over 6 months (p<0.05) but comparison of IOP reduction with other groups (Inter-group) Eg. DT vs LT, was not significant (*p>0.05) [Table/Fig-4].

Safety of the Medications

All three combinations studied were safe with no major adverse drug reactions (ADR) warranting discontinuation/withdrawal of medications. We observed 47 ADRs over 6 months of follow up among 3 groups (n=101). Since none of the ADRs were serious, ADRs posed no threat to compliance to the medications. Minor ADRs were managed by Ophthalmologist and reassurance was given.

DISCUSSION

As we know, POAG is chronic disease with life-long treatment in almost all cases. Treatment of POAG has been a great cause of concern, in terms of diagnosis [10], outcome, treatment & poor quality of life [11,12]. Though the recommended drug treatment typically starts with single drug and eventually progresses to combination of drug therapy, in "The Collaborative Initial Glaucoma Treatment Study [6]" it was as high as 75% at the end of two years.

We in India, lack pharma co-economic data on POAG, for that matter Glaucoma as whole. But in developed countries lot of research has been focussed on pharmaco economics, especially in health insurance sector where any new drugs need to be proven cost-effective before they are included in reimbursement list of drugs [13].

Unlike Western countries, pharmacotherapy is relatively cheaper in India, but still many cannot afford. A study on insurance claims in USA by Lee et al., [14] found out that the mean POAG-specific charge per person/year was $1570, with a median charge of $840. Interestingly, only the pharmacy charges accounted for 25% of the POAG-specific charges. Patients in our study spent about mere Rs. 1544, 2567 & 3876 per year per eye for BT, DT & LT group respectively (drug cost and transport charges). Despite of such a huge difference in the expenditure on drugs, our experience during the study has been that, a large number of patients could not afford drugs, especially LT. Cost of the drugs was one of the main compliance factor observed in our study. Other factor included patient's attitude towards the disease, where patients did not appreciate the seriousness of POAG in early stages, even though early detection and treatment of POAG may provide a substantial cost savings to the health care system [15,16]. The POAG is insidious and asymptomatic except in very late stages of the disease and it was the main reason why many patients eligible for study, refused to take prescription for POAG.

We observed in our study that the treatment with DT is less cost effective than with BT. The DT combination was prescribed twice a day and they were more costlier than BT. The efficacy of DT, in reducing mean IOP at the end of 6 months (7.83 mm Hg) was less than that of BT (9.38 mm Hg). Therefore, BT is clearly a better combination in our study in terms of being less costly and more efficacious than DT. A literature review conducted by Hommer A et al., [17], found out that fixed drug combination of brimonidine and timolol or brimonidine adjuvant to timolol was cost-effective than fixed drug combination dorzolamide and timolol or dorzolamide adjuvant to timolol in European countries over a period of three and twelve months of follow-up.

There are very few studies being done on cost effectiveness/analysis of POAG medications in Indian set-up. Jothi et al., [18] reported a higher per year expenditure (Rs. 3438/year) on DT combination compared to our study (Rs. 2562 ± 15.74/year). In another study conducted in India [19] where they studied yearly cost of drug/eye of single drugs like brimonidine and bimetaprost, but the data is still useful to have an insight into the costs incurred during treatment of POAG with BT. The cost of brimonidine was Rs. 1147.75 ± 11.15/year/eye, whereas addition of timolol to brimonidine in our study, the cost incurred was Rs.1544 ± 32.06/year/eye.

Cost analysis of individual anti-glaucoma drugs i.e. latanoprost, brimonidine, dorzolamide, pilocarpine, timolol used in POAG was done by Navreet et al., [20] revealed higher spending on drugs than in our study where patients were prescribed combination of drugs. Timolol was reported to be cheapest among them, costing Rs. 423.4/year for both eyes. Latanoprost, brimonidine, dorzolamide without the combination of timolol cost Rs. 8840.3, 3416.4, Rs. 2379.8 per year for both eyes, respectively. One of the possible explanations could be that maximum retail price (MRP) varies with different brands/generics. Cost of medication also depends on P-drug (Personal drug) of a prescriber.

The treatment expenditures including pharmacological costs and non-pharmacological costs were too high in developed countries compared to developing country like India. In 2011 Lafum et al., [21] studied UK General Practitioner Research Database (UK-GPRD) for costs of three anti-glaucoma medications, one of them was LT. The study revealed that each patient on LT spent about £ 203.64 per year on LT medication. Patients in our setup spent only about Rs. 3876/year, albeit, 8.6% of per capita/annum income of the family, on their LT medication. Though spending on medications in patients of UK cannot be compared with current spending by our patients, it only indicates relatively less financial burden of drugs on our patients. Many patients coming to government hospitals often could not sustain this expenditure. The daily cost of glaucoma medications was calculated in China [22] was also higher than from our study.

Overall, despite having lower costs of glaucoma medications compared to developed countries, we observed, patients in our set up are reluctant to adhere to medications.

Current study provides basic costs (cost of drugs and cost travel) incurred by the patients in government hospitals, which was devoid of consultation fees for doctors, diagnostic and monitoring charges etc. since the infrastructure for diagnosing and monitoring of POAG are not widely available in India, especially in primary and secondary levels of health care systems, the cost of the treatment is expected to be same or higher, especially when POAG is treated in private hospitals.

Further studies are needed to focus on cost-effectiveness by taking more objective parameters using perimeter, monitoring of POAG progression using fundus camera, which can provide observable changes in POAG, over long period.

Because of lack of data on drug loss during drug administration we assumed it to be as one drop/day. But with the improvements in dropper tips in recent years, the drug loss during administration may be minimal in future studies. With drugs cost is expected to come down in coming years [23] in addition to improvements in drug delivery methods, the glaucoma pharmacotherapy is expected to be more cost effective in future. The cost of drug treatment in India is cheaper unlike in developed countries like UK [24], Australia [25]& USA [26].

LIMITATIONS

The current study has several limitations. We assumed that patients were compliant to medications and did not measure the compliance directly by any objective methods. Nevertheless, we tried our best to find out the compliance by asking indirect questions regarding drug usage. We also assumed that amount of drug loss during administration as one drop per day in our set up. While calculating for costs for transport, we only considered charges incurred by patients. We did not include additional costs of attender, if there was any. We hardly observed any outsider patient coming alone. Most of them came with an attender, thus including their expenses would have given better picture about money spent for treatment. Cost incurred to reach bus-stop of native place of the patient from their home was not included. Other expenses like daily earning, lunch, snacks etc were not included.

CONCLUSION

The BT combination was found to be cost-effective and the efficacy is comparable LT at the end of 6 months. The costs of the drugs and travel expenses are main factors contributing to POAG costs in our study. With better availability of infrastructure for glaucoma screening, diagnosis and treatment at secondary and primary health care set-ups, financial burden of POAG on the patient can be reduced.

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