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Research Article

MEDICAL THERAPY OF GLAUCOMA-A PHARMACO-ECONOMIC ANALYSIS

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Abstract: **Background:** This pharmaco-economics study was conducted to determine and compare 3- monthly and yearly cost and cost-effectiveness of various anti-glaucoma drugs; Latanoprost 0.005%, Bimatoprost 0.03%, Travoprost 0.004%, Pilocarpine 2%, Dorzolamide 2%, Brimonidine 0.2%, Timolol Maleate 0.5%. **Methods:** The number of drops in five new bottles were counted and then averaged for each drug. The effectiveness data was number of millilitres of IOP reduction as compared to baseline. The MRP, drop count and IOP reduction data were used to calculate the 3- monthly and the yearly cost and cost-effectiveness of the study drugs. **Results:** According to the study results the rank order of drugs with respect to yearly cost was Latanoprost (Rs.8840.3) >Travoprost (Rs4620.9) >Dorzolamide (Rs.3416.4) > Bimatoprost (Rs.2927.3) > Brimonidine (Rs.2379.8) > Pilocarpine (Rs.1204.5) > Timolol (Rs.423.4). The drugs in order of cost-effectiveness are timolol> pilocarpine> bimatoprost> brimonidine> travoprost> dorzolamide> latanoprost. **Conclusion:** On the basis of MRP, number of drops per bottle and average IOP reduction, Timolol had the most favourable cost-effectiveness amongst the study drugs. Among the Prostaglandin analogues, Bimatoprost was the most cost-effective followed by Travoprost and Latanoprost. The alfa- 2 agonist Brimonidine was found to be less cost-effective than Bimatoprost. From the cost-effectiveness point of view, Timolol should be used as first line therapy where not contraindicated and Bimatoprost followed by Brimonidine reserved as alternatives.

Key words: Cost-effectiveness, Glaucoma, Intraocular pressure, Pharmacoeconomics, Yearly cost.

INTRODUCTION

Glaucoma is a major public health problem, being the largest cause of bilateral blindness, second only to the cataract[1]. Over 8.4 million people were estimated to be bilaterally blind from primary glaucoma in 2010, expected to rise to 11.1 million by 2020. Previous estimates based on blindness prevalence surveys suggested that 12% of world blindness (4.4 million people) was caused by glaucoma. From 2010 to 2020, the most detectable change in glaucoma worldwide will be its increase in India. The largest absolute number of glaucoma cases was in China, followed by Europe and India[2,3]. Glaucoma is a "silent killer", being asymptomatic till presentation to the ophthalmologist, by the time it becomes irreversible[4]. The World Health Organization recommended to its member countries to combat this public health problem through a program approach[5]. Glaucoma has been added in the disease control strategy of the VISION 2020 initiative[6]. Progression of glaucomatous changes leads to visual impairment, making glaucoma the second leading cause of blindness. As the global burden of glaucoma is high and predicted to rise as major cause of ocular morbidity; study of economic aspects of glaucoma are required[7]. For judicious utilization of scarce health care resources, economic evaluation of available treatment strategies is done.

Economic evaluation is the comparative analysis of treatment options in terms of their costs (resource use) and benefits (health effects). Health economists have shown an increasing interest in evaluating cost-effectiveness of available treatment strategies[8]. Cost-effectiveness is measured by dividing therapy's total cost by its therapeutic effectiveness which may be cure rate, remission rate or treatment success. Cost-effectiveness i.e cost per unit treatment success may be a more relevant measure of cost than drug average wholesale price[9]. A cost-effectiveness comparison of two hypothetical drugs is shown in the table-1. Drug A (AWP Rs 200) and drug B (AWP Rs 240) showed success rates of 10 units and 20 units respectively. The cost-effectiveness of drug A would be Rs 20 per unit treatment success while of drug B would be Rs 12 per unit treatment success which concludes drug B to be more cost-effective than drug A inspite of being more costlier.

Table 1: Cost-effectiveness Calculation

	DRUG A	DRUG B
Cost/effectiveness or success rate	Rs 200/10UNITS	Rs 240/20 UNITS
Cost-effectiveness	Rs 20 per unit treatment success	Rs 12 per unit treatment success

The cost-effectiveness of a hypothetical drug A is compared with drug B making assumptions about treatment success rates.The above calculation shows drug B to be more cost-effective than drug A inspite of being costlier.
While chosing a treatment strategy, cost-effectiveness should also be taken into consideration for lowering the economic burden and improving patient compliance. Incremental cost-effectiveness ratio (ICER) is the cost to achieve additional treatment success and a low value of ICER indicates a treatment strategy being more efficient from pharmaco-economic viewpoint[10]. ICER is used to compare the drug being considered for substitution with the existing standard treatment[11].

The analytical tools of economic evaluation like cost-effectiveness are most valuable with respect to chronic diseases like glaucoma with many alternative treatments[12].Treatment strategies of glaucoma aim at lowering IOP which helps to prevent optic nerve damage and glaucoma related blindness. Even a single unit lowering of IOP has been associated with significant clinical improvements[13].

Pharmacotherapy being the first line of treatment for elevated IOP, the five major classes of antiglaucoma drugs are: [14]

- Beta-adrenergic antagonists
- Adrenergic agonists
- Carbonic anhydrase inhibitors
- Cholinergics
- Prostaglandin analogues

As glaucoma management requires life-long therapy and the options available are many, economic evaluation helps the ophthalmologist choose the best treatment strategy[15]. So, the objective of this economic evaluation is to estimate the cost-effectiveness of various anti-glaucoma medications used in india.

METHODS

The proprietary names of drugs used in the study are Xalatan 2.5ml (Latanoprost 0.005%), Lumigan 3ml (Bimatoprost 0.03%), Travatan 2.5ml (Travoprost 0.004%), Pilocar 5ml (Pilocarpine 2%), Dorzox 5ml(Dorzolamide 2%), Alphagan 5ml (Brimonidine 0.2%), Iotim 5ml (Timolol Maleate 0.5%).

This economic evaluation to calculate the 3-monthly and yearly cost-effectiveness of various anti-glaucoma medications used two types of data inputs:

1. Cost for various drugs – The yearly and three-monthly cost of various drugs was calculated from MRP after calculating the number of drops per bottle and cost per drop.

2. Effectiveness - The number of millimeters of mercury of IOP reduction after a three month therapy.

Sources of cost

Five bottles of each commercially available size of anti-glaucoma drugs were taken from a retail shop. The maximum retail price of each drug was noted. The actual, not the labeled volume was determined for each bottle at 25˚C by emptying the entire contents in 5 ml cylinder holding the vial at 135˚ angle. Simultaneously the number of drops per vial were also counted.

Daily Cost of a particular anti-glaucoma medication was calculated by dividing the cost of one bottle by total number of drops in a bottle and multiplying by number of drops required daily. It was assumed that all the patients were treated for both eyes.
Medication per day (both eyes) bottle
Yearly cost = cost per day × 365
Cost for three months= yearly cost / 4

Effectiveness (Lowering of Iop)
IOP lowering efficacy of each drug was calculated from retrospective analysis of cases of POAG/ OHT on monotherapy with these drugs. The effectiveness data used for this economic analysis was number of millimetres of mercury of IOP reduction compared with the baseline. Percentage lowering of IOP was also determined by the formulae:

Percentage fall in IOP = (Fall in IOP/Baseline IOP) x 100

Table 2: Cost inputs - MRP of topical antiglaucoma drugs

Latanoprost 0.005%	**Rs 1187**
Bimatoprost 0.03%	Rs 432.53
Travoprost 0.004%	Rs 652
Pilocarpine 2%	Rs 49.90
Dorzolamide 2%	Rs 208
Brimonidine 0.2%	Rs 198.8
Timolol Maleate 0.5%	Rs 40

Table 3: Effectiveness Data

DRUG	BASELINE IOP(mm Hg)	IOP AT 3 MONTHS (mm Hg)	FALL IN IOP (mm Hg)	PERCENTAGE FALL IN IOP
Latanoprost	27.4	18.9	8.5	31%
Bimatoprost	26	17.6	8.4	32.3%
Travoprost	24.9	16.3	8.6	34.5%
Pilocarpine	23.8	18.1	5.7	23.95%
Dorzolamide	24.6	19.7	4.9	19.9%
Brimonidine	24.7	18.4	6.3	25.5%
Timolol	25.86	19	6.86	26.53%

Cost-Effectiveness

Cost-effectiveness of the drug was calculated by dividing the 3-monthly cost of drug by 3-monthly IOP reduction. Thus cost of the drug per mm Hg reduction of IOP was calculated. Cost-effectiveness is the cost per mm lowering of IOP while percentage cost-effectiveness is the cost per percent lowering of IOP.

3- monthly cost-effectiveness = cost of drug for 3 months/IOP reduction in 3 months

Cost per percent reduction of IOP was also calculated.

Cost-effectiveness (%) = cost of drug for 3 months/percentage reduction of IOP

The yearly cost-effectiveness was thus c

alculated by mutiplying the figures obtained by above formulaes by four.

Table 4: Cost Analysis of Anti-Glaucoma Drugs

DRUG	AVERAGE DROPS PER BOTTLE	COST PER DROP(Rs)	DROPS PER DAY PER EYE	COST× 3MONTHS BOTH EYES(Rs)	YEARLY COST BOTH EYES(Rs)
Latanoprost	98	12.11	1	2210.08	8840.3
Bimatoprost	108	4.01	1	731.82	2927.3
Travoprost	103	6.33	1	1155.24	4620.9
Pilocarpine	90	0.55	3	301.12	1204.5
Dorzolamide	133	1.56	3	854.1	3416.4
Brimonidine	122	1.63	2	594.95	2379.8
Timolol	137	0.29	2	105.85	423.4

Table 5: Cost-Effectiveness Data

DRUG	AVERAGE IOP REDUCTION FOR 3 MONTHS (mm Hg)	% LOWERING OF IOP	CE FOR 3 MONTHS (Rs/mm fall)	% C.E FOR 3 MONTHS (Rs per % fall)	CALCULATED YEARLY CE (Rs/mm fall)	CALCULATED % YEARLY CE (Rs per % fall)
LATANOPROST	8.5	31%	260.01	71.30	1040.04	285.2
BIMATOPROST	8.4	32.3%	87.12	22.66	348.48	90.64
TRAVOPROST	8.6	34.5%	134.33	33.48	537.32	133.92
PILOCARPINE	5.7	23.95%	52.83	12.57	211.32	50.28
DORZOLAMIDE	4.9	19.9%	174.31	42.92	697.24	171.68
BRIMONIDINE	6.3	25.5%	94.44	23.33	377.76	93.32
TIMOLOL	6.86	26.53%	15.43	3.99	61.72	15.96

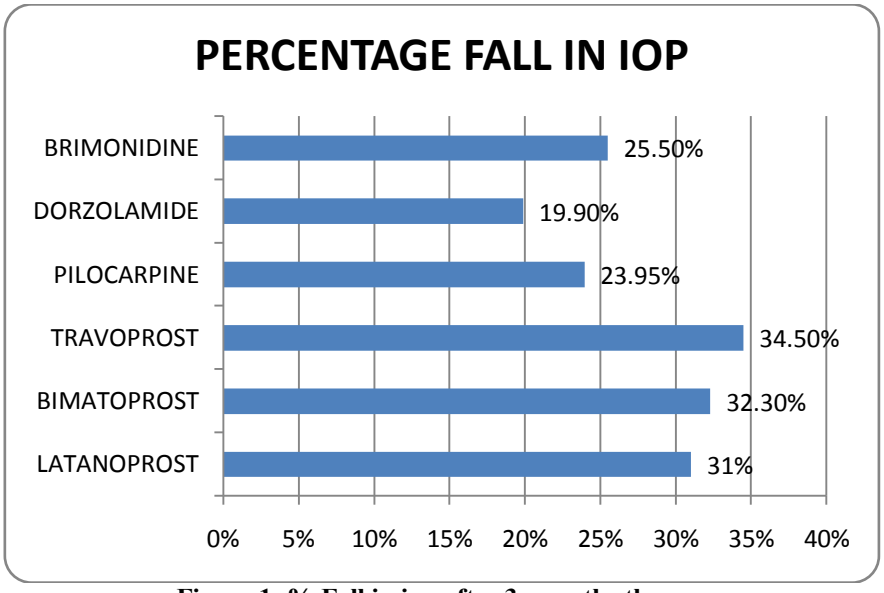

Figure 1: % Fall in iop after 3- months therapy

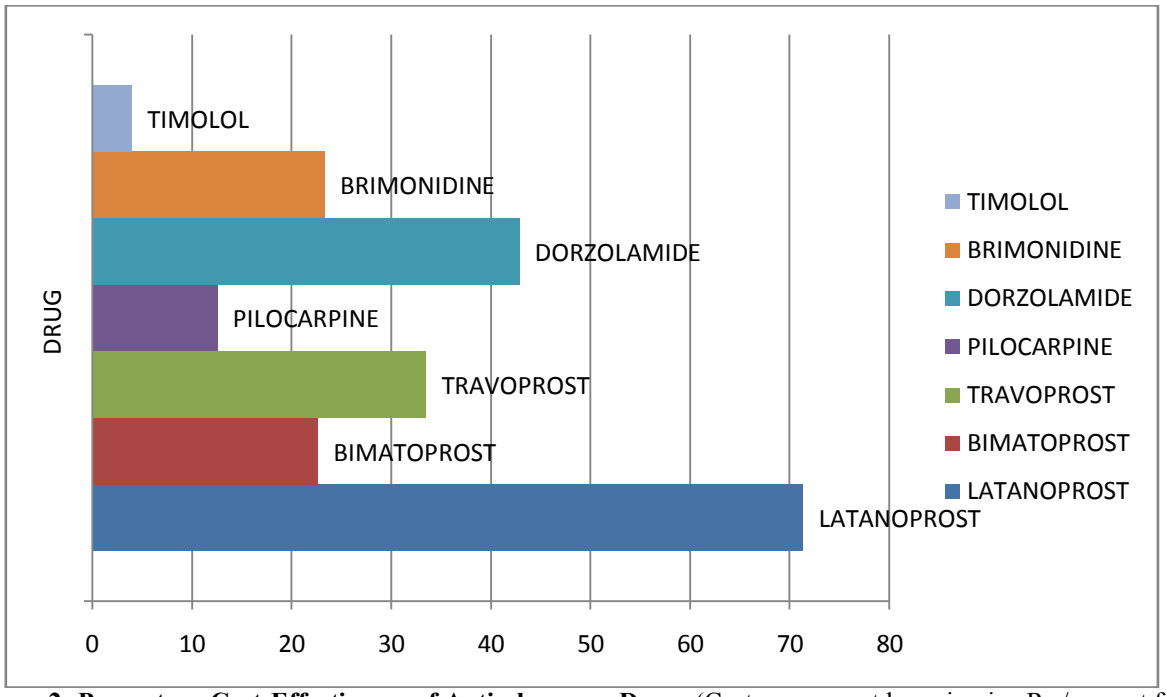

Figure 2: Percentage Cost-Effectivenes of Anti-glaucoma Drugs (Cost per percent lowering i.e. Rs./percent fall)

DISCUSSION

Glaucoma is a chronic disease requiring a lifelong therapy. With limited resources and a variety of therapeutic choices, glaucoma therapy is moving towards cost-effective decision making. To be able to make intelligent therapeutic choices, cost and effectiveness of the therapy need to be incorporated into a single parameter. Thus in the present study, the final decision making pharmaco-economic tool is cost-effectiveness i.e. cost per mm IOP reduction. The idea of this study is to update physicians regarding the cost-effectiveness apart from daily and yearly cost of treating glaucoma with topical medications. Our study addresses the calculated cost-effectiveness passed on to the patient treatment plans and does not address the issues of tolerability, safety and persistence. It is notesworthy, that each study drug has its own frequency of side effects and withdrawl rates which may increase the cost of treatment. As the study is cross sectional, the above factors could not be incorporated. The study does not take into account the support programmes offered by various drug companies. According to our study, overall the most cost-effective option is timolol> pilocarpine> bimatoprost> brimonidine> travoprost> dorzolamide> latanoprost. However the increasing order of MRP‘s gives a different picture timolol< pilocarpine< brimonidine< dorzolamide< bimatoprost< travoprost< latanoprost.

Prostaglandin analogues (Hypotensive lipids) bimatoprost, travoprost and latanoprost comprise the most prescribed

class of anti-glaucoma drugs. They are more effective than timolol but also costlier with overall cost-effectiveness being higher for timolol. The implications of these results could be, using timolol as the first line therapy with PG analogues being reserved for patients showing intolerance or inappropriate clinical response. Hypotensive lipids (HTL's) have high efficacy, a favourable safety profile, ease of once daily regimen and are often reasonable on a cost per day basis. Thus they have become a favourite among both physicians and patients despite their higher costs. Ultimately, the goal of eye care providers is to give the best, most cost-effective care to their patients. Drug efficacy, tolerability, medication response, compliance and dosing regimens are the factors that may justify a decision to prescribe a more costly medication.

Amongst the PG analogues analysed in our study, bimatoprost offers the lowest annual costs and the greatest cost-effectiveness. Pharmacoeconomic comparison of the commonly prescribed alfa-2 agonist, brimonidine and the most cost-effective PG analogue, bimatoprost show contrary results with respect to annual costs and cost-effectiveness. Brimonidine has a lower annual cost as compared to bimatoprost, but it is preferable to prescribe the later as it has a more favourable cost-effectiveness due to higher efficacy and convenient once daily dosing. Several prior studies have analyzed the economics of medically managing glaucoma. In 1983 Gottlieb et al. designed a model to evaluate the cost-effectiveness of various screening methods in subjects aged 40–79 years[16]. Frenkel et al conducted a cost-effectiveness pharmacoeconomic analysis of prostaglandin and prostamide therapy for patients with glaucoma or ocular hypertension was at an eye institute at Miami, and bimatoprost was found to be most cost-effective amongst the group followed by latanoprost and travoprost eye drops[17]. The previously published cost-effectiveness study by Holmstrom et al comparing timolol, bimatoprost and latanoprost monotherapies and with add on therapy; was based on data from published clinical trials. They concluded that the most cost-effective strategy was to use timolol as first-line therapy and to add bimatoprost if therapeutic efficacy was not reached[18].

The drug manufacturers have tried to device several ways to counter the effects of wasting with many methods like overfilling of the bottles and bottle design modifications. In the last few years, manufacturers have improved the bottles and dropper tip designs so that there is less wastage by producing smaller drop sizes, such that only one drop is dispensed. So, a lot of preparations may be cheaper, but due to large drop size, they may end up less cost-effective. The MRP of an anti-glaucoma agent is just one of the multitudes of factors to consider when choosing a medication for a patient. The products with higher actual volume, smaller drop size; hence, larger number of drops per ml may in reality cost less. Thus in this study yearly costs of antiglaucoma drugs have been calculated from cost per drop, thus taking into consideration factors such as drop size, number of drops per bottle, overfilling, underfilling and dosage regimen along with MRP of the vial.

Effectiveness of drug is another deciding criterion for choosing the appropriate drug therapy for glaucoma patients. A comparitively expensive drug may have the benefits of higher IOP reduction and better compliance thus placing the drug at a superior position from cost-effectiveness point of view. Thus the parameter of effectiveness has been incorporated into this study as the fall in IOP with therapy.

Taking into consideration, the broadening gap between therapeutic possibilities and resources available,the choices have to be made by prioritising (rationing) all treatment strategies[19]. Economic evaluation of glaucoma therapy needs to be targetted at assessment of efficiency i.e. health effects weighed against the sacrifices or costs incurred for attaining them.The deciding criterion should be cost-effectiveness of treatment strategy rather than efficacy or cost alone [19, 20].

CONCLUSION

Timolol appears to be the best treatment option amongst the study drugs from cost-effectiveness point of view. Hypotensive lipids (Prostaglandin analogues) should be reserved for patients showing intolerance or inappropriate therapeutic response to timolol. Amongst HTL's in the study, bimatoprost was the most economical followed by travoprost and latanoprost when evaluated in terms of cost-effectiveness. Bimatoprost is superior to the alfa-2 agonist brimonidine inspite of being costlier, due to favourable cost-effectiveness.

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