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Original Research Article

An observational study on the effectiveness & safety of anti-glaucoma medications in treatment naive patients of primary open angle glaucoma

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ABSTRACT

Background: The paradox of open angle glaucoma therapy lies in the loss of reported efficacy of drugs when they are studied for real world effectiveness. Studies related to effectiveness and safety done in a longitudinal fashion in new cases of open angle glaucoma are scant. This study was undertaken to address the shortcomings in this regard.

Materials and Methods: This was an open label, prospective, observational study. The patients were taken up for the study at their baseline visit and 3 subsequent follow up visits for next 6 months. The effectiveness was gauged on the basis of average IOP changes from baseline. Each patient was administered questionnaires for ocular surface disease and interviewed for possible adverse drug reactions at each follow up.

Results: There were 68 participants who completed the study. All these patients reported at baseline and 3 subsequent follow ups. The mean baseline IOP was 27.20 (SD ±6.29) mm of Hg and this reduced considerably to 16.97 mm of Hg (SD ±3.18) which was a 37.61% reduction from the baseline ($p < 0.05$). The best reductions of IOP were noted in prostaglandin analog & β blockers either in fixed dose combinations. There were 37 episodes of adverse drug reactions reported. All of them were definitely preventable and mild in severity.

Conclusions: The prostaglandin analogs remain the most important anti glaucoma drugs as far as effectiveness is concerned. The safety profile of most of the drugs was marred by deterioration the ocular surface disease score. The use of preservatives was also associated with statistically significant worsening.

1. Introduction

The pharmacological agents used in management of POAG are broadly classifiable as miotic medications, alpha adrenergic agonists, beta blockers, carbonic anhydrase inhibitors and prostaglandin analogs (PGAs). Amongst the anti- glaucoma medications, beta-blockers (timolol) and prostaglandins (latanoprost, bimatoprost and travoprost) have been found to be most effective in lowering the intraocular pressure (IOP).[1,2] The PGA however have been demonstrated to have better efficacy than beta blockers.[3] The effectiveness of these groups of drugs needs to be widely and repeatedly studied in order to provide inputs for future trends in the management of POAG as trial data about efficacy does not always translate into same effectiveness in the real world scenario.

The long term use of anti-glaucoma medications has a major safety issue, in the form of ocular surface disorders

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(OSD). OSD affects up to 59% of patients with glaucoma.[4] This high prevalence may result from both conditions being increasingly common in the elderly; in addition, preservative-containing topical medications, especially those used chronically, can exacerbate or contribute to OSD. Benzalkonium chloride (BAK) in particular reduces the stability of the precorneal tear film, with direct corneal toxicity[5] this has been shown in vitro and in vivo in animal and human studies.[6,7] All classes of topical pressure lowering medications cause ocular surface discomfort, especially topical carbonic anhydrase inhibitors (CAI). Topical medication–related OSD contributes to worse symptoms, poorer adherence, worse surgical outcomes, and reduced quality of life in glaucoma patients. Apart from topical therapy, oral acetazolamide and methazolamide are also a part of the armamentarium against glaucoma. The patients on glaucoma therapy present with multitude of systemic side effects (bradycardia, bronchial spasm, accentuation of heart block and CCF) and ocular side effects (conjunctival hyperemia, iris pigmentation, hypertrichosis, periocular pigmentation, uveitis, foreign body sensation, irritation, stinging, dryness of eyes). With an increasing burden of this disease, especially in the elderly, there is a need to monitor the adverse drug reactions (ADR) of anti-glaucoma medications to find out the variety, intensity and frequency of such reactions for better prescription guideline formulation.

2. Materials and Methods

This was an open label, prospective, observational study. Enrolment of patients was done after obtaining approval from the institutional clinical research ethics committees and was carried out for a period of 6 months. Each patient was followed up for a period of 6 months.

2.1. Inclusion criteria

The study included all newly diagnosed patients of POAG (Age ≥40 years) belonging to either genders receiving any type and any number of anti-glaucoma medication. POAG was defined as mean IOP greater than 21mmHg, with typical glaucomatous optic disc changes and demonstrable visual field defects with reliability indices within acceptable limits along with wide open angles on gonioscopy. Visual acuity ≥6/60 (20/200) was considered included. Those able to give consent for participation and well comprehend the pre-tested questionnaires were considered for the study.

2.2. Exclusion criteria

The study excluded those having pre-existing hyperaemia and dry eye disease, history of any ocular surgery or laser procedure, patients suffering from any other form of glaucoma, ocular inflammation or infection in the preceding 3 months, diabetes mellitus, hypertension, pregnant or lactating women, patients those are sensitive to preservatives, any other concomitant eye drops like lubricants or corticosteroids and one eyed patients. Concurrent use of other ophthalmic medications, contact lenses, conditions precluding Goldmann applanation tonometry and uncooperative patients were also excluded.

Techniques included were history taking, clinical examination under slit lamp, applanation tonometry, Gonioscopy, 90D Biomicroscopy and Humphrey's standard automated perimetry for the management of primary open angle glaucoma. The demographic data collection was performed with the help of a suitable case report form which will include all relevant information

For effectiveness the baseline IOP values were recorded on the day of drug allocation. There were two IOP measurements recorded and if the measurements differed by >2 mmHg, a third measurement was also be taken. The mean of 2 or 3 readings were recorded as the baseline value. The mean IOP measurements for both eyes were taken and both were used for analysis in patients who will have disease in both eyes and satisfy the inclusion criteria. During each subsequent visit, the same protocol of IOP recording was followed.

Systemic side effects: The patients were screened for bradycardia, bronchial spasm, heart block and CCF, syncopal attacks, paraesthesia, anorexia, hypokalemia, acidosis, malaise, depression, bitter taste, lethargy, sleepiness and other possible unknown side effects from their treatment history.

Ocular side effects: The patients were also be asked for presence of common ocular side effects are conjunctival hyperemia, iris pigmentation, hypertrichosis, periocular pigmentation, uveitis, foreign body sensation, irritation, stinging, dryness of eyes, corneal hypoaesthesia, allergic blepharoconjunctivitis, blurring of vision, thickening and darkening of eye lashes, ocular and periocular pain (headache,) twitching of the eyelid, fluctuating myopic shift in refraction, decreased vision in dim illumination, cataract, punctal stenosis and corneal oedema.

Ocular surface disorder: The ocular surface disease index (OSDI) is based on a 12-item questionnaire assessing symptoms related to chronic dry eye, their severity, and impact on the patient's ability to function within the last week. Each item is scored from 0 to 4: 0 signifies symptoms none of the time, 1 signifies symptoms some of the time, 2 signifies symptoms half of the time, 3 signifies symptoms most of the time, and 4 signifies symptoms all of the time.[8] The OSDI overall score ranges from 0 to 100, with higher scores indicating worse OSD. A score of 0 to 11.9 was considered normal; 12 or greater was used as a marker of OSD.[9]

Categorical variables were expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence

of Attributes. Non parametric variables were expressed as Mean and Standard Deviation and compared across the groups using Friedman's Test. Parametric variables were analysed by repeated measures ANOVA. The statistical software SPSS version 20 has been used for the analysis. An alpha error level of 5% was taken, i.e. if any p value is less than 0.05 it was considered as significant.

3. Results

With reference to demographics majority of enrolled subjects were men (60.29%) and the average age was 58.16 years (± 9.35 years S.D.). The majority of patients were in the decade of 61-70 years of age. The mean baseline IOP was 27.20 (SD ±6.29) mm of Hg and this reduced considerably to 16.97 mm of Hg (SD ±3.18) which was a 37.61% reduction from the baseline ($p < 0.05$) (table 1). The highest IOP reductions from baseline were noted in the groups receiving combination therapy of PGA+BB (39.14%), CAI+BB (38.78%) and combination polytherapy PGA+CAI+BB (36.56%) at the end of the study (Figure 1). Monotherapy with PGAs (33.43%) performed better over BBs (26.30%) as far as overall IOP reduction was concerned.

There were 37 episodes of adverse drug reactions reported in the entire duration of this study. There 25 ocular adverse drug reactions and 12 systemic adverse drug reactions. All of them were DEFINITELY PREVENTABLE and MILD in severity. Analysis revealed that 80% systemic adverse drug reactions and 72% of ocular adverse drug reactions were of POSSIBLE nature whereas 20% systemic adverse drug reactions and 28% ocular adverse drug reactions were of PROBABLE nature as per Naranjo's algorithm. There were 17 patients had a single ADR, 14 patients reported 2 ADRs, 4 patient had 3 ADRs and one patient had 4 ADRs.

There was a significant worsening of OSDI scores from baseline to the conclusion of the study. Monotherapy with prostaglandin analogs despite having a reported a few cases of ADRs, returned the best scores and carbonic anhydrase inhibitors were the worst performers as far as OSD scores were concerned. The use of BAK (preservative) revealed a statistically significant difference from preservative free drop users as far as OSDI was concerned.

Table 1: Mean Intraocular Pressure in respective visits

Visit no.	Mean Intraocular Pressure(mm of Hg) [Mean (SD)]	Reduction From Baseline (%) mm of Hg	p Value
1	27.20 (±6.29)	-	
2	17.36 (±4.97)	9.84 (36.17%)	<0.001^{s}
3	16.75 (±4.58)	10.45 (38.42%)	
4	16.97 (±6.07)	10.23 (37.61%)	

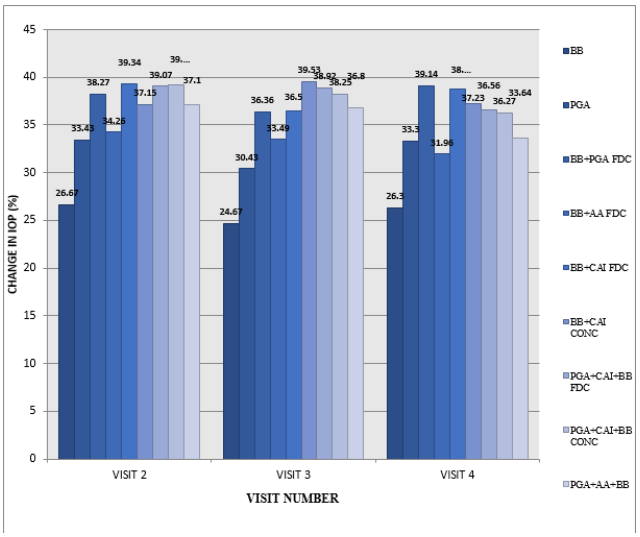

Fig. 1: Changes in mean IOP per drug group over all follow up visits

Table 2: Ocular ADR across visits

ADR	Visit 2 (FU 1)	Visit 3 (FU 2)	Visit 4 (Final)
Dryness	07	03	03
Redness	07	04	04
Foreign body sens.	02	00	02
Watering	03	00	01
Stinging	01	00	01
Blurring	00	00	01
Itching	03	02	03

Table 3: Systemic ADR across visits

ADR	Visit 2 (FU 1)	Visit 3 (FU 2)	Visit 4 (Final)
Headache	02	01	01
Dyspepsia	01	00	00
Dyspnea	01	00	00
Bitter taste	02	01	01
Dry mouth	01	01	00
Lethargy	01	00	00

Table 4: Mean OSDI score in various Visits

	Mean OSDI Score [Mean (SD)]	p Value
Visit 1 (baseline)	NA	
Visit 2 (FU 1)	7.44 (2.85)	0.001^{S}
Visit 3 (FU 2)	7.20 (3.15)	
Visit 4 (final)	8.48 (2.88)	

* Friedman's test for non parametric variables

Table 5: Per Drug group side effects

Drug Combination	No. of side effects												
	Systemic S/E						Ocular S/E						
	Head ache	Dyspepsia	Dyspnea	Bitter taste	Dry mouth	Lethargy	Dryness	Redness	Forgn body	Watering	Stinging	Blurring	Itching	Dark lash
BB	1	0	1	0	0	1	3	0	1	0	1	0	2	0
PGA	0	0	0	2	0	0	2	5	1	1	0	0	1	1
BB+PGA	1	0	0	0	0	0	1	1	0	2	0	0	2	0
AA+PGA	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BB+AA	1	0	0	0	2	0	0	0	0	1	0	0	0	0
BB+CAI	1	0	0	0	0	0	3	5	2	0	1	1	1	0
PGA+CAI	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PGA+CAI+BB	0	1	0	1	0	0	4	4	0	0	0	0	2	0
PGA+AA+BB	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PGA+CAI+AA	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PGA+CAI+AA+BB	0	0	0	0	0	0	0	0	0	0	0	0	0	0

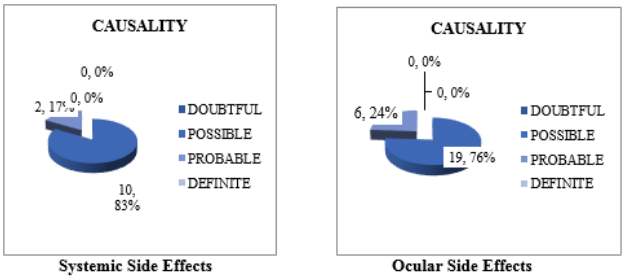

Fig. 2: Overall ADR naranjo causality assessment

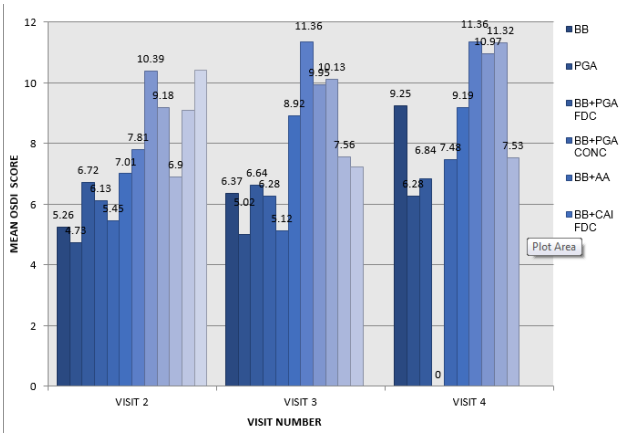

Fig. 3: Mean OSDI scores per visit

4. Discussion

The mean baseline IOP was 27.20 (SD ±6.29) mm of Hg. This was in line with a few landmark studies like CIGTS,[10] but higher than the EMGT[11] and OHTS.[12] This may be due to stringent exclusion criteria in those trials where IOP > 30 mm of Hg were excluded. Further analysis reveals that eyes in stage 1 (mean 23.56 mm of Hg) & stage 2 (mean 25.36 mm of Hg) were having much lower mean IOPs than stage 3 (mean 28.54 mm of Hg) or stage 4 (mean 31.34 mm of Hg). All the follow up visits showed a statistically significant overall reduction of IOP from baseline with visit 4 showing a mean IOP of 16.97 mm of Hg (SD ±3.18) which was a 37.61% reduction from the baseline. The maximum reduction was noted for visit 3 which was 16.75 mm of Hg, a 38.42% reduction over the baseline IOP. Stage wise analysis revealed all the eyes had a statistically significant reduction of IOP from baseline. The duration of follow up visits (6 weeks) was sufficient to allow us to study changes in effectiveness.

Therapeutic effectiveness vide IOP reduction was a principal outcome of this study and the major findings were that monotherapy with PGAs (IOP reduction 33.43%) or PGA containing FDCs with BB (IOP reduction 39.14%) scored much better than most other options. Individuals on timolol or other BB achieved a reduction of 26.30%

from the baseline. All these reductions were statistically significant. There may be a number of reasons for the better effectiveness of PGA containing regimens – convenient once daily dosing, better adherence, better side effect profiles and clinically proven efficacy are just a few. CAI+PGA therapy achieved an overall reduction of 37.55% and AA+BB combinations achieved a reduction of 31.96%. These findings are in agreement with previously published literature.

Ocular surface disease index (OSDI) scores were noted at all follow up visits for all the patients. This study showed that the mean OSDI score kept significantly ($p < 0.05$) deteriorating from Visit 2 to Visit 4. The percentage of cases with OSD (score > 12) increased progressively from 5.88% in Visit 2, 8.82% in Visit 3 and 16.18% in Visit 4 with statistical significance. The above are in consonance with reported literature. Expectedly, stage 4 patients had the worst OSDI scores due to the greater number of drugs being used simultaneously.

Drug wise analysis showed that the worst performers were patients who received CAIs in any combination which has been reported by Skalicky et al.[13] Monotherapy with PGAs had the best OSDI scores over the entire duration of the study. Even combination therapy of PGA+BB had similar good scores. The same group of drugs when prescribed in combination yielded better scores than when prescribed concurrently.

The use of BAK also correlated well with higher OSDI scores and patients without BAK scored better in all 3 follow up Visits ($p < 0.05$) which is what has already been reported by Fechtner et al[14] and Katz et al.[15]

Analysis of ADRs with respect to drugs revealed that there were 10 events due to monotherapy with PGAs (27.03% of ADRs: 11.63% of all PGA prescriptions, n=86), 7 events were due to BBs (18.92% of ADRs: 7.69% of all BB prescriptions, n= 91), 6 events were due to PGA+BB+CAI (16.21% of ADRs: 5.17% of all PGA+BB+CAI prescriptions, n=116), 6 events were due to CAI+BB (16.21% of ADRs: 17.65% of all CAI+BB prescriptions, n= 34), 4 events were due to PGA+BB (10.81% of ADRs: 3.67% of all PGA+BB prescriptions, n=109) and 4 events were due to AA+BB (10.81% of ADRs: 8.69% of all AA+BB prescriptions, n=46). These findings may reflect the fact that the prescriptions of BBs & PGAs in isolation or combination were higher than the other drug groups. The regimens containing CAI were incriminated in high percentages across almost all their regimens. The 5 instances of ocular ADR where the drug was substituted featured CAI containing regimens 3 times and were substituted by AA in all cases. PGA monotherapy with latanoprost lead to darkening of eyelashes and was substituted by AA+BB combination therapy. BB monotherapy with Timolol lead to dyspnea in one case and was substituted with Bimatoprost. Almost all of the other ADRs due to PGA or BB containing regimens were self-limiting in nature.

5. Conclusion

The findings of this study corroborate the fact that prostaglandin analogs either in monotherapy or in fixed dose combinations with timolol remain the most important anti-glaucoma drugs as far as effectiveness is concerned. The safety profile of most of the drugs was fairly unremarkable. The ocular surface disease score worsened progressively. Available regimens with beta blocker, alpha2 agonist or prostaglandin analog fared relatively better and are potentially better tolerated. The use of BAK as a preservative was also associated with statistically significant worsening of scores so preservative content should be a major consideration while writing prescriptions. The advent of newer drugs for glaucoma management is on the horizon but the proven effectiveness and safety of previous drugs still retain therapeutic significance in decision making.

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8. Conflict of Interest

The authors declare they have no conflict of interest.

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