Review Article

Lessons Learned from Landmark Studies in Glaucoma

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Abstract

Background: Glaucoma is a disease characterized by progressive optic neuropathy that can be caused by a variety of etiologies, including both primary and secondary mechanisms, with the main modifiable risk factor being high intraocular pressure (IOP). Visual field defects, along with structural and functional changes, are typically seen. It is one of the leading causes of blindness worldwide, and as the proportion of those over age 40 increases, so will the prevalence of glaucoma.

Purpose: This article aims to provide a brief review of the important early glaucoma studies with abundant evidence and thus guide us in our management decisions.

Methods: We reviewed diagnostic criteria used by landmark glaucoma clinical trials, which were prospective, multicenter, masked, randomized control trials. We included trials that were concerned mainly with open-angle glaucoma.

Result and conclusion: Landmark studies have demonstrated that lowering IOP is of benefit in preventing the onset of glaucoma in ocular hypertension and in reducing disease progression in eyes with primary open-angle glaucoma (POAG) but do not suggest that the degree of protection is related to the degree of IOP reduction.

Keywords: Disease progression, Intraocular pressure, Primary open angle glaucoma, Visual field.

Introduction

The landmark studies offer the best scientifically tested information to improve decision making that is evidence based medicine (EBM). The landmark studies in primary open-angle glaucoma include the following:

- Ocular hypertension treatment study (OHTS)
- Early manifest glaucoma trial (EMGT)
- Collaborative initial glaucoma treatment study (CIGTS)
- Collaborative normal tension glaucoma study (CNTGS)
- Advanced glaucoma intervention study (AGIS)

These studies also test various risk factors for the progression of glaucoma. Let us attempt to answer some of the lead questions from our colleagues in day to day clinical practice in the light of these landmark studies.

Q1. When should the treatment be initiated for ocular hypertension?

Ocular hypertension treatment study (OHTS)[1] was carried out with the following aims:

- To determine if topical medications delay or prevent glaucoma in ocular hypertension.
- To identify the risk factors.

OHTS summary:

- Study was conducted on 1636 subjects aged between 40 and 80 years.
- Intraocular pressure was 24 to 32 mmHg in one eye and 21 to 32 mmHg in the other eye.
- All the subjects had normal discs and fields.
- The exclusion criteria: any disease that can cause VA/VF/ Disc deterioration.
- The subjects were randomized into:
  - Observation group (n = 819) and
  - Treatment group (n = 817) who received medication achieved 20% drop and IOP of below 24 mmHg.
- Subjects are monitored by stereo disc photographs yearly and visual fields 30-2, 6 monthly.

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- Deterioration on VF and /or optic disc was the end point[1].
- After 5 years of follow-up, it was observed that 9.5% cases in the observation group and 4.4% cases in the treatment group progressed to glaucoma.

Ocular Hypertension Treatment Study (OHTS) Phase 2: The rationale

The OHTS phase 1 established that medication reduces the incidence of POAG but it does not indicate when to initiate treatment and if all the OHT cases should receive early treatment.

In OHTS phase 2, the cases were divided into two groups; the early treatment group (n = 694), where medication continued in the treatment group and Delayed treatment group (n = 672) where medication was initiated in the observation group after 7.5 years. No difference was observed between early and delayed treatment groups with regards to the cumulative incidence of POAG at 13 years.

The risk factors:

- The central corneal thickness < 555 microns,
- IOP > 26 mmHg and
- C: D > 0.4 were identified as important risk factors for progression from OHT to POAG.
- The higher PSD and older age were also the risk factors.

The absolute risk reduction with treatment was also studied. In the high risk group, the risk was reduced from 42 to 19%, whereas in the low risk group, the risk was reduced from 7 to 4%.

Lessons learned from OHTS:

- Take risk factors into account before initiating therapy.
- If no risk factors, just observe.
- Treat those with the thinner cornea (<555), Higher C; D (>0.4), IOP >26, older age and high PSD.

For calculation of risk of glaucoma progression in ocular hypertension, one can use the OHTS risk calculator available online; http://www.discoveriesinsight.org/glaucomarisk.htm

Q2. My newly diagnosed patient of POAG stopped anti-glaucoma medication. What will happen to his vision?

Early manifest glaucoma trial (EMGT) compared immediate treatment vs. No treatment for newly diagnosed POAG.[2]

EMGT summary:

- Glaucoma diagnosed by reproducible VF defects.
- The study included cases of NTG and pseudo exfoliation glaucoma (PXG).
- Exclusion criteria were MD >16 db, IOP > 35 mmHg or VA < 20/40.
- RCT of 255 patients aging between 50 and 80 years and randomized to:
  - No treatment group
  - Treatment group; all the patients received ALT and Betaxolol. Latanoprost added if IOP was > 25 mm Hg in the treatment group.
- End point was a progression of field and/or disc changes.[2]
- After 6 years of follow-up, in no treatment group and 62% of cases showed progression in the treatment group 45% cases showed progression. Thus the absolute risk reduction with treatment was found to be 17%.

The risk factors:

- Baseline factors
  - Pseudo exfoliation
  - Older age
  - Higher IOP
  - MD - 4 db or worse
- Follow up factors
  - IOP; each 1-mmHg reduction from baseline reduced risk of progression by 10%.
  - Disc hemorrhages.

Lessons learned from EMGT -

- Treatment effect validated. Every mm reduction matters.
- Disease progression is variable; follow closely; reset target as needed.
- Aggressive treatment for patients with high risk factors.

Q 3. Which is better, surgery or drops?

The collaborative initial glaucoma treatment study (CIGTS) aims:

- To compare the effect of topical drugs *vs*. trabeculectomy on early diagnosed OAG.
- To compare impact of glaucoma and its treatment on quality of life.

CIGTS summary:

- Prospective study on 607 cases of POAG, pigmentary glaucoma and PXG.
- Subjects were randomized to medical management and trabeculectomy arms.
- The target IOP is customized for each patient.
- The primary end point was a progression of VF loss.[3]

In the surgical group, there was increased risk of visual loss initially due to cataracts, but by the end of 4 years, both groups showed similar results.

The sub group analysis showed that initial surgery is a better option for subjects with advanced VF loss as it reduces the IOP fluctuation.

VF progression is influenced by several factors (measured before initiation of treatment), that includes age (older age), VF loss, diabetes mellitus and extent of IOP fluctuation.[3]

Lessons from CIGTS (Table 1).

- Discuss treatment options with the patient.
- Surgery first in patients with moderate or advanced disease.
- Results support current practice of medical treatment first.

Table 1: CIGTS – Results at 5 years

	Medical Treatment	*Surgical Treatment*
IOP reduction	From 28 mmHg to 17–18 mm Hg i.e., 35%	From 27 mmHg to 14–15 mmHg i.e., 40%
VF deterioration at 5 years	Comparable	Comparable
Quality of life	Comparable	Comparable

Q 4. Do I need to treat all my NTG cases?

The collaborative normal-tension glaucoma study (CNTGS)[4] aims:

- To know if IOP plays a part in the etiopathogenesis of NTG.
- To learn about the untreated natural history of NTG.

CNTGS summary:

- A total of 240 patients recruited who had:
  - IOP <21 in 10 baseline measurements
  - Glaucomatous cupping.
  - Corresponding VF defects.
  - Angles open.
- History was recorded and examined to exclude one-time damage, hemodynamic crisis, arterial obstructive disease, sleep apnoea and neurological diseases that mimic similar fundus picture, shock induced optic neuropathy, arteritic AION or orbital mass-causing atrophy.
- Only those eyes were randomized who had:
  - Documented disease progression or
  - VF defect threatening fixation.
- One hundred and forty such eyes were randomized to:
  - Treatment n = 61 (Drops, ALT or surgery to achieve 30% reduction in IOP)
  - No treatment n = 79
- The subjects were followed up 5 years.

Chart showing glaucoma progression risk with and without treatment

CNTGS results:

- Progression in untreated NTG is highly variable (Figure 1). Half of the cases did not progress in 5 years despite no treatment.
- Factors that are associated with progression are:
  - Female
  - Migraine
  - Disc hemorrhages.
- Overall, lowering IOP in NTG slows progression.

Lessons from CNGTS -

- Distinguish between progressive and non-progressive NTG.
- Surgery may not be necessary.
- Aggressive treatment if- Female, migraine or disc border hemorrhages.[4]

Q5. Which treatment is better; laser or surgery for advanced glaucoma cases who have failed on medical treatment?

Advanced glaucoma intervention study (AGIS) aims to know the:

- The outcome of laser and surgical interventions in eyes that have failed on medical treatment (Goal IOP <18)
- Association between control of IOP after surgical intervention and VF deterioration (Figure 2).

AGIS summary:

- Study was carried out on 789 eyes (451 black and 327 white) of POAG who had uncontrolled IOP with topical medications. These eyes were randomized into two groups:
  - Trab → ALT → Trab (TAT) i.e. Trab first, then ALT, and then Trab if needed
  - ALT → Trab → Trab (ATT) i.e. ALT first, then Trab and then trab if needed
- Medical treatment was given as required.
- The cases were followed for at least 5 years.
- The primary outcome measure was decreased vision (VA or VF).[5]

AGIS results:

- In Blacks, vision better with ALT first.

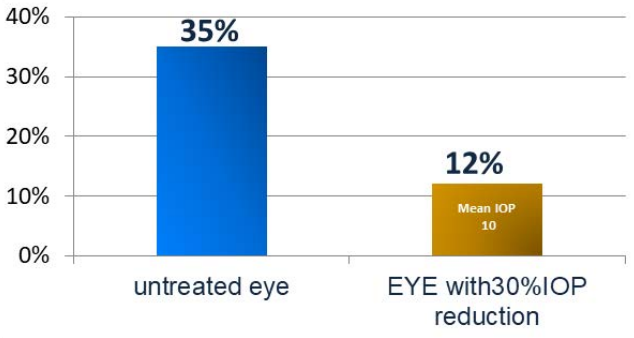

Figure 1: Risk of progression with and without treatment in NTG

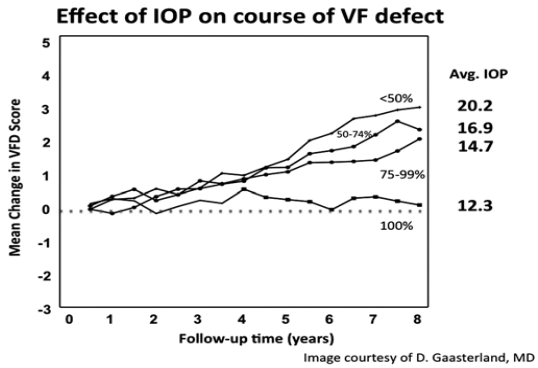

Figure 2: Effect of IOP on visual field defect

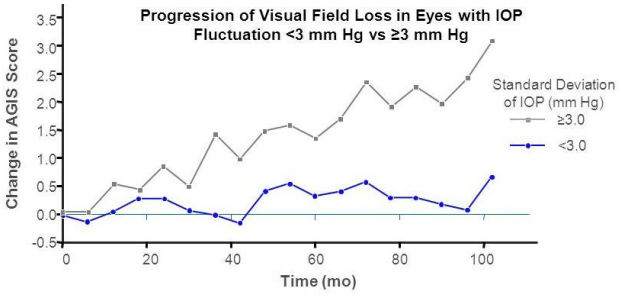

Figure 3: Effect of IOP fluctuation on progression of visual fields loss

Table 2: Risk of progression as indicated by different studies

Diagnosis	*Risk of progression without treatment (%)*	*Risk of progression with treatment (%)*
OHT (OHTS 5 years)	9.5	4.4
NTG (CNTGS 6 years)	35	12
Early POAG (EMGT 6 years)	62	45
Advanced POAG (AGIS 7 years)	NA	30 VA 14 VF (with IOP <15 mm Hg)

- In whites, vision is better with ALT first for the initial 4 years and then better in the surgery group.[5]

Thus,

- Blacks should have laser first.
- Whites should have trab first.

The side arm looked at IOP and VF loss. The cases were divided into 4 groups:

- IOP <18 mmHg at 100% visits.
- IOP <18 mmHg at 75–100% visits.
- IOP <18 mmHg at 50–75% of visits.
- IOP <18 mmHg at <50% visits.

Associative analysis

The associative analysis indicated that in advanced glaucoma, lowering IOP to low teens means most of the cases will not progress.

Each mm (SD) fluctuation in IOP increases risk by 40% (Figure 3). So keep the IOP fluctuation (Standard deviation) less than 3 mm Hg. Trab controls IOP fluctuation better.

The overall risk of cataracts was 78%.

DM and higher age were other risk factors.

Lessons from AGIS -

- Take race into account when choosing therapy.
- IOP > 18 and wide IOP fluctuation means an increased risk of VF progression.[5]
- Older age and DM are other risk factors.

The following table summarizes the risk of progression as indicated by different studies (Table 2).

Conclusion

- lowering of IOP by every mmHg helps in prevention of glaucoma progression (EMGT).
- If IOP is maintained in lower teens, most glaucoma patients will not progress (AGIS).
- Many cases of NTG do not progress. If they progress, the only proven method of treatment is IOP lowering.
- Not all ocular hypertensives need treatment; assess the risk on an individual basis and discuss with the patient.

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