Clinical Decisions in Glaucoma: An Evidence Based Approach

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Glaucoma

- Important topic
- Numbers of patients with glaucoma
  - Current over 2 million
  - Projected 3.36 million by 2020
  - Estimates ½ not aware
- Identification of patients is critical
- Optometrists capable of diagnosis and management

Glaucoma

- Optic nerve condition with characteristic structural changes and associated vision loss
- Commonly encountered in practice
- Advances in understanding pathophysiology, diagnostic abilities and therapeutic options

Where does intraocular pressure fit in the diagnosis and management?

Does pressure matter?

- Historically IOP always linked with glaucoma
- Chandler, 1960 – 20 may prove to be too high for a damaged nerve
- Armaly et al 1980 – increased risk of glaucoma damage over range of IOP from low teens to mid-20’s
- David et al increased risk with increased IOP above normal range

Does Pressure Matter?

- Collective experience tells us yes
- Experience shows us higher IOP more damage
  - Unilateral cases or monocular pressure elevation
  - Asymmetric IOP with asymmetric damage
- Literature shows more stability with lower and more stable IOP control; more progression with higher IOP
- IOP not the best tool to diagnose but is a consideration
3376 Patients Observed in NEI and GRF Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Dx</th>
<th>Randomization</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>EMGT1</td>
<td>255 pts</td>
<td>OAG</td>
<td>Tx (ALT + betaxolol) vs observation</td>
<td>4-9 years</td>
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<tr>
<td>OHTS2</td>
<td>1636 pts</td>
<td>OHT</td>
<td>Medical Tx vs observation</td>
<td>5 years</td>
</tr>
<tr>
<td>CIGTS3</td>
<td>607 pts</td>
<td>OAG</td>
<td>Medical Tx vs surgery</td>
<td>5 years</td>
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<tr>
<td>AGIS4</td>
<td>738 eyes</td>
<td>OAG</td>
<td>ALT vs surgery</td>
<td>8 years</td>
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<tr>
<td>CNTGS5</td>
<td>140 eyes</td>
<td>NTG</td>
<td>Medical Tx and/or surgery vs observation</td>
<td>7 years</td>
</tr>
</tbody>
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**Glaucoma Update**

- IOP is still the primary risk factor in the effective treatment of Glaucoma
- Lowering IOP decreases the risk of glaucoma progression

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**How Often Does Glaucoma Progress?**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow Up</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic Based</td>
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<tr>
<td>OHTS</td>
<td>126 pts</td>
<td>5 yrs</td>
<td>40%</td>
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<tr>
<td>EGPS</td>
<td>1081 pts</td>
<td>5 yrs</td>
<td>43.4%</td>
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<tr>
<td>DGIS</td>
<td>126 pts</td>
<td>7 yrs</td>
<td>N/A</td>
</tr>
<tr>
<td>EMGT</td>
<td>255 pts</td>
<td>6 yrs</td>
<td>45%</td>
</tr>
<tr>
<td>CNTGS</td>
<td>140 Eyes</td>
<td>7 yrs</td>
<td>32%</td>
</tr>
<tr>
<td>AGIS</td>
<td>747 Eyes</td>
<td>8-13 yrs</td>
<td>28.1%-32.5%</td>
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</table>

Population Based

St. Lucia 205 pts 10 yrs N/A 52%-73%

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**Glaucoma Progression**

- It is common

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**Tania: 44 y/o Hispanic Female**

- Has been seen several times over the yrs for routine eye care
- 1998: TA 20/22
- 09/05: TA 18/20
- 12/07: 19/20

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**Tania: 44 y/o Hispanic Female**

- 12/08: TA 25/21
- Pach: 610/620 µ
- OCT done 1/5/08 – for review
- 4/20/09: TA 23/24
- 4/19/10: TA 23/25
- 10/11/2010: TA 22/23

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5/3/12
Tania

- Ocular HTN
  - No treatment
  - Is there a reason to justify treating her?
- What is her risk for developing glaucoma?
  - 5 yrs vs. lifetime?

Ocular Hypertension Treatment Study (OHTS)

- Long-term randomized, multicentered controlled, clinical trial
- Evaluate safety and efficacy of topical meds in delaying or preventing the onset of VF loss and/or nerve damage
  - Can we identify patients at greater risk?

Issues Relevant to Tania

- What is his risk of actually developing glaucoma in 5 yrs?
  - Observation group: 9.5%
  - Treatment group: 4.4%
- From OHTS:
  - Depends mostly on corneal thickness...?
    - IOP of 25.75 mmHg
      - Ave Corneal thickness < 556 µ: 36% Risk
      - Corneal thickness 565 to 588 µ: 13%

POAG Risk Over 5 Years by Central Corneal Thickness and Baseline IOP in Observation Group

POAG Risk Over 5 Years by Central Corneal Thickness and Baseline Vertical C/D Ratio in Observation Group

OHTS
*Arch Ophthalmol*
June 2002;120:701-713

- 55% of POAG endpoints involved ON changes in the absence of VF endpoint
- EMGT: < 10% progressed based on ON
  - > 90% progressed based on VF
Risk Factors POAG
Arch Ophthal June 2002;120:714-720

- Thin corneas
- Age
- Cup-disc ratio
- IOP
- Race – but African Americans had thinner corneas and greater vertical C/D ratios
  - Sig in Univariate analyses (59% greater risk), not sig in multivariate analysis
  - Reduced PSD at baseline (need multiple VF’s)

OHTS

- Careful consideration of individual patients
- Not everyone requires treatment
- Some risk factors development of glaucoma are vertical cup: disc, level of IOP; central corneal thickness

Rogelia 62 y/o Hispanic Female

- CC -> pain/burning in the both eyes c/w dry eye
- VA: 20/20 OU
- Ant Segment unremarkable
- TA: 12 OU
- Fundus

Rogelia 62 y/o Hispanic Female

- Inferior thinning RE
- H: 0.5X V 0.6

Rogelia 62 y/o Hispanic Female

- Visual field abnormalities
Rogelia - Summary

- 63 y/o Hispanic Female presents with dry eye complaints
- Suspicious Cups RE inferior thinning and a superior nasal field defect RE (Normal LE), consistent with OCT RNFL findings, IOP 12
- Diagnosis -> NTG RE, No GL LE
- Management…Tx vs NoTx

Normal Tension Glaucoma

- Chronic optic neuropathy exhibiting characteristic optic disc cupping and visual field loss
- Untreated IOP in statistically normal range
- No secondary causes for optic neuropathy
- No accepted level of IOP below which the diagnosis becomes “Normal Tension”
- 20 to 50% of patients with POAG have IOP within statistically normal range

NTG: The Big Question?

- What is the relationship between IOP and visual field loss?
- Is there a benefit of lowering IOP in patients with normal tension glaucoma?

Collaborative Normal Tension Glaucoma Study

- Collaborative effort of 24 research and medical centers around North American and Europe
- Study conceived in 1984 out of the Glaucoma Research Foundation meeting
- Enrolled 230 patients
  + 140 eyes of 140 patients met randomization criteria. 90 excluded (38%)

NTG Study Criteria

- Only patients with progressive disease were enrolled, or fixation was threatened
- 20 and 90 years old
- No previous recorded IOP of >24 mmHg
- 4 week washout period from previous meds
- 10 baseline IOPs, 6 between 8 am - 6pm in 1 day, 4 reading other days
  + Median IOP had to be ≤20
- 3 Baseline VFs
NTG Study Criteria

- Enrolled 1 eye per patient
- Used better eye and excluded advanced disease
- Randomize threats to fix immediately
- Patients randomized:
  - Untreated control group
  - Tx group with a 30% IOP reduction
    - Beta adrenergic blockers, adrenergic agonists excluded b/c cardiovascular and crossover affects
- Endpoint defined as progression
  - Progressive VF loss or ON changes

CNTGS

_Am J Ophthalmol_ 1998;126:487-497

- 230 enrolled: 140 eyes met criteria, were randomized
  - 90/230 (39%) excluded - never progressed
- 61 Treatment group, 79 observation group
- Untreated group: 35% progressed, 65% no progression
- Treatment group: 12% progressed
- Longer time to progression in tx’d eyes

NTG Study: Natural History


- 160 subjects (of the original 260) that were initially not treated
  - 1/3 showed localized progression in 3 yrs
  - Rate of progression was variable
  - 50% showed progression 5-7 yrs
  - > 50% not treated show no progression
  - Conclusion: Rate progression highly variable

NTG General Considerations

How should we manage NTG?

- Because many pts showed no progression
  - Wait to treat, until rate of the disease can established
- For those in high risk groups, watch more closely
  - Women with history migraine, and disc hemorrhages are at the highest risk for progression
  - Asian and men had the least risk for progression
- For those with advanced disease: Treat more aggressively

How Low Does IOP Need to Be?

Advanced Glaucoma Intervention Study (AGIS)

- To assess long-range outcome in sequence of interventions in Trab vs ALT in eyes who have failed initial med therapy
- Study being done b/c varying degrees of success with either procedure.
- Eyes randomized:
  - trab followed by ALT followed by trab (TAT)
  - ALT - trab - 2nd trab (ATT)
    - May use antifibrotic agents on 2nd surgery
AGIS

- Multicenter randomized clinical trial
- 789 eyes of 591 patients inadequately controlled on med therapy
- Randomized to 2 treatment sequences
  - ATT or TAT
  - Additional sequences offered after failure
  - Antifibrotic agents later in study

AGIS: IOP and Field Loss

- 789 eyes followed for 6-11 years
- 4 analysis groups based on how often IOP < 18
  - 100% visits
  - 75-99%
  - 50-74%
  - < 50% of visits

Report # 7 AJO Oct 2000

AGIS: IOP and Field Loss, Report # 7 AJO Oct 2000

AGIS

- Long-term IOP fluctuation was associated with progression

Ophthalmology Volume 111, Number 9, September 2004

Reanalysis AGIS: IOP Fluctuation Important in Pts With Low Mean IOP

Which IOP is Most Important?

- Mean IOP
- Pressure during the night
- IOP over 24 hours
- Peak IOP
- Fluctuation in IOP
- Overall variability
**Forest vs. Trees**

- I don't really care
- The challenge:
  - Diagnosing early
  - Making sure patients understand the disease
  - Make sure patients are compliant
  - Follow closely to determine the rate of progression

**Luisa: Hispanic Female Initial Presentation**

- Presented for routine exam
  - VA: 20/20 OU
  - TA: 26 OD; 27 OS
  - Gonioscopy – CBB 360 OU, No PAS
  - ON: 0.55 – 0.6 OU Inferior notch

**Louisa Hispanic Female Initial Presentation**

**Luisa: IOP: 26/27 mmHg**

- What should her initial management be?
- How low does the pressure need to go?
  - What is the basis for starting medical therapy?
- Is there any argument that could be made for not treating?
- What is the risk of blindness?
- If we don’t treat her – will she go blind?
- At what rate will she lose visual field?

**Early Manifest Glaucoma Trial**

- Randomized clinical trial to assess the effect of immediate tx on progression compared to no initial or delayed tx
- Identify factors related to progression
- Study natural history
Early Manifest Glaucoma Treatment Study (EMGT)

- NEI supported clinical trial performed in Sweden
- Does early treatment alter the natural course of the disease in OAG?
- Early POAG, PDG, PXF, NTG
- Randomized:
  - ALT and Betaxolol vs. Careful Observation

EMGT

- 255 OAG patients (POAG, NTG, EFG)
- 129 randomized to 360 ALT & betaxolol
- 126 randomized to observation
- Mean age 68 years old
- 66% women
- Mean baseline IOP 20.6

EMGT

Follow up visit with VF q 3 mos; disc photos q 6 mos
Progression monitored with
  - Full threshold VF with Glaucoma Change Probability (using pattern deviation values)
  - Flicker chronoscopy of nerve photos, side by side comparison for suspected change

EMGT Results

Arch Ophthalmol 2002;120:1268-1279

- Median f/u 6 years
- Average decrease IOP in Tx’d group 25% or 5.1mmHg
- 53% progressed -> 47% did not progress
- Progression slower in the Tx group
  - Longer time to progression in the tx’d group
    - Median time to progression 18 mos longer in tx’d group
    - 45% (58/129) Tx’d v. 62% (78/126) control

EMGT Progression

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Un treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Yr Progression</td>
<td>44%</td>
<td>66%</td>
</tr>
<tr>
<td>8 Yr Progression</td>
<td>59%</td>
<td>76%</td>
</tr>
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</table>
**EMGT**
Baseline factors that predicted progression on a multivariate analysis:
- Higher IOP
- Exfoliation
- Worse MD
- Older age
- Frequent disc hemorrhages


**Lessons from the EMGT**
- Treatment works…
- Average rate of progression was 2.3 dB over 10 yrs
- Rate of progression was decreased by 10% for every 1 mmHg reduction of IOP
- NonTx Group: 1/3 of pts 6 yrs out still have no progression

**Recommendations for Management from the EMGT**
- Newly Dx pts should be followed often
- Take more VF’s early – establish rate of progression – up to 7 VF over 2 yrs
- Pts with rapid progression should be vigorously treated
- Tx should be tailored for each patient

**Lessons from the EMGT**
- Average age of defect discovered -> 72 yo
  - Most pts at this age will not go blind or get any disability from blindness
- Average 70 yo patient diagnosed with glaucoma is expected to live 12 years
- He/she will loose ~ 4.2 dB during his remaining lifetime
- This patient will likely not “get in trouble” unless he starts with MD of < 10 dB

**Lessons from the EMGT**
- Low Risk Patients
  - Patients with early stage disease…and
  - Low IOP’s
    - Is at low risk for rapid progression
    - Tx affect is rather small
  - May leave room for recommending close follow up with no treatment
  - Elderly w/ unilateral Dz also considered low risk

**Glaucoma Treatment**
- Once diagnosis is made, decision to lower IOP follows
- Selection of target IOP
  - Consider extent and rapidity of damage
  - Consider IOP and other risk factors
  - Gain insight from recent studies
  - Treatment is arbitrary and individualized
- Medications, laser therapy, surgery
- Follow-up
### Target IOP

- Individualized to patient
  - Initial IOP, extent, rapidity of damage
  - Existing damage is clue to risk of future damage
  - Aggressive decrease if worsening at one level

- Advanced damage strive for low normal range
- Consider family history, age and fellow eye

- IOP not great for identifying those with glaucoma but is important in management and follow up care.
- There is a benefit to IOP reduction in glaucoma management
- More advanced damage and/or more rapid onset or progression calls for more aggressive IOP reduction

- Monocular trials when possible
- Consider switch before adding med
- If not at goal move on
- Be aggressive with IOP reduction in advanced cases or when there is evidence of progression
- Baseline info is critical
  - Pre-tx IOP, Level of IOP at times of progression
  - VF and nerve appearance

### Chop or Drop

Several studies have questioned traditional beliefs regarding treatment:
"Are we in fact harming our patients by delaying surgery until there is evidence of further field loss, and/or deterioration while utilizing medical and laser regimens."

- Does medical therapy/ALT provide as good longterm control of IOP as surgery in preventing continued field loss?
- Is medical therapy truly benign?
- Is the overall “quality of life” better with standard medical therapy or with surgical intervention?
Better IOP Control with Surgery

- 168 newly diagnosed untreated patients with POAG (1983-84) followed 4 yrs
  - Standard medical therapy
  - ALT
  - Trabeculectomy
- Consistently lower IOP in Surgical group
  - Surgery: 13.3
  - Medical: 16.8
  - Laser: 17.8

Better IOP Control with Surgery 1st

- Success of IOP control:
  - Surgery: 98%
  - Medical: 80%
  - Laser: 60%
- VA worse in surgery group by 1/2 line
- Incidence of cat = 4%


Better IOP Control with Surgery

- 52 POAG patients
- Randomized to medical Tx vs Scheis trabeculectomy
- Subdivided medical group
  - Well controlled on simple meds
  - Need for surgical intervention
  - Follow up 6-8 yrs


Surgery 1st Argument

Better Long-term IOP Control

- 99 pts randomized to Surgery vs Medical therapy
- Medical therapy further randomized:
  - Successful IOP control with medicine
  - Those who failed medical therapy and needed surgery
- Better IOP control in surgery group (15 vs 20.8)
- Surgery 1st eyes were less likely to lose field
- Many of med Tx eyes ultimately needed further surgery – 53%


Surgery 1st

Better Long-term IOP Control

- Better IOP control with surgery
- Less field deterioration
- Similar VA
- Poor results for patients who needed surgery after medical therapy failed


Surgery as Initial Treatment for POAG: Better IOP Control

- Medical therapy followed by trab
- Primary trab followed by supplemental med tx
- Follow up 4.6 years
- Lower and better IOP control
- Sig. more field loss with medical therapy
- No significant difference in VA


Surgery 1st Argument
Can medical Tx be Harmful?
- Loss of visual field while waiting for IOP control
- Jay/Allen, Smith showed worse field preservation in patients who failed medical therapy and later went on to need surgery

Is Medical Therapy Harmful?
- Less success with filter after medical therapy fails (Lavin et al)
  - 98% success with primary trab
  - 79% success with trab when medical therapy fails

Is Medical Therapy Harmful?
Direct adverse reaction to drops
9/78-12/85 32 deaths directly from T5
- Other Reactions
  - Aplastic anemia
  - Respiratory effects
  - CNS problems
  - Loss of libido
  - Lathargy
- CAI’s: Renal and GI effects

Quality of life
- Compliance
  - 76% objective yet subjective report 98%
- Older patients are on more multiple meds for other conditions. More complicated regimens lead to less compliance
  - GLT showed only 30% of patients were controlled on a single beta blocker
  - More visits result in worse quality of life

Summary: Surgery 1st
- Safe
- Better IOP control
- Good if not better field preservation than med Tx
- VA is at least as good
- Cost effective

Collaborative Initial Glaucoma Treatment Study (CIGTS)
- Purpose: To compare the long-term effect of treating newly diagnosed POAG with standard medical vs. filtration surgery
  - 607 pts w/ mild to moderate glaucoma randomized b/w Oct 93 – April 97
  - IOP lowering goal: 35% decrease from baseline
  - 5 year follow-up
CIGTS Results
- Both groups had substantial/sustained ↓ in IOP
- Baseline mean IOP = 27 mmHg
- Medical therapy IOP reduced to 17.6 mmHg
  - 37% reduction
- Surgical therapy: IOP reduced to 14 mmHg
  - 52% reduction

CIGTS and IOP
- VF loss did not differ by Tx
- Surgery 2-3 mmHg less than Medical
- Surgery group had > VF loss and > VA loss in 1st 3 yrs, but equal by yrs 4-5


CIGTS: Visual Fields and Cataract
- 10-12% of subjects in both groups progressed over 5 yrs
- Rate of cataract development greater surgery group


CIGTS: Quality of Life
- Both groups satisfied
  - Surgery: more local eye symptoms, irritation
    - Most disappeared by yrs 4-5
  - Medical: variety of systemic symptoms, but not consistent over time
    - Clearly different from surgery Sx


CIGTS: Conclusion
- Both surgery and medicine as initial Tx result in the same VF outcome at 5 yrs
- An IOP lowering of 35% seems to be optimal in mild glaucoma with no net decline in visual function
- The greater IOP lowering in the surgery group was of no further benefit

CIGTS: Conclusion
- Investigators do not recommend changes to current approaches of management
- Longer follow up is needed as this is a chronic disease
  - 5 yrs is not adequate time to draw conclusions
CIGTS
Bottom Line

- At 5 yrs, no difference between surgery and medicine for control of IOP
- The study legitimized surgery as a primary procedure for treating newly diagnosed GL
  - When all was said and done – surgery resulted in lower IOP vs. Medicine
  - Safe
  - Overall in the long-term – may prove be better