Management of Progressive Normal-tension Glaucoma

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Treatment of normal-pressure glaucoma: Collaborative Normal Tension Glaucoma Study (CNTGS) showed feasibility of observing patients; ophthalmologist must determine whether progression present, whether progression related to intraocular pressure (IOP), to what degree IOP should be lowered, and expected outcomes of treatments.

Visual fields: ophthalmologist should beware of altering management based on single change in visual fields; worsening should be confirmed by series of examinations that consistently demonstrates deterioration; in CNTGS, progression declared if patient showed change on 2 of 3 visual field tests performed in 1 mo and on 2 of 3 visual field tests at next visit; findings on visual field tests vary within same patient, especially in patients with existing damage.

Relationship between pressure and progression: theories — variations in manifestations of glaucoma (from normal-pressure glaucoma through ocular hypertension) may represent spectrum of susceptibility of optic nerve; alternatively, some investigators believe that normal-pressure glaucoma and ocular hypertension distinct entities and that damage not related to IOP; lowering IOP may not help patient if damage independent of pressure; evidence — offered by study of 18 patients with bilateral disease; in eyes treated with filtration, mean IOP reduced by 30% and no significant change observed in slopes on visual fields; in contrast, fellow eyes worsened; in another study, mean IOP decreased from 16 to 9.2 mm Hg after treatment and decrease in slope stabilized; in CNTGS, when IOP reduced by ≥30%, only 20% of patients worsened; in control arm, 60% worsened; Early Manifest Glaucoma Trial (EMGT) showed more modest benefit from treatment; in CNTGS, patients most likely to benefit from treatment included those without disc hemorrhage at baseline and women; family history of glaucoma, presence of cardiovascular or ischemic brain issues, and damage at baseline also influenced efficacy.

Level of intraocular pressure: reduction of ≥30% desirable based on EMGT and CNGTS; in study evaluating latanoprost, mean diurnal reduction in IOP 19% and mean reduction at 3 wk 21%; reduction most pronounced in patients with highest IOP at baseline; difficult to lower IOP to <8 to 10 mm Hg; in another study, average diurnal reduction in IOP 17% and maximum reduction 19%; 30% reduction in IOP difficult to achieve in patients with low IOP at baseline; another study found that average trough IOP fell by 14% and that timolol and latanoprost had similar effects; in another study, latanoprost superior to timolol based on early-morning IOP; brimonidine has modest effect; peak effect of brimonidine similar to that of latanoprost, but brimonidine cannot produce 30% reduction in IOP; in another study, 19% reduction in highest 2 pressures achieved with brimonidine, but only 25% of patients achieved 25% reduction in IOP.

Trabeculectomy: in EMGT, patients treated with trabeculectomy plus betaxolol achieved 18% decrease in IOP; in older study, 46% of patients achieved 20% reduction in IOP, and one-third of patients achieved IOP of 12 mm Hg; however, loss of effect observed over time.

Trabeculoplasty: reduction in IOP of 30% to 43% reported; however, hypotony or maculopathy reported in 1 out of 8 patients; nonrandomized study of first trabeculectomies evaluated patients managed without antiproliferative agents, with intraoperative 5-fluorouracil (5-FU), and with intraoperative mitomycin C (MMC); rate of success higher in patients receiving antiproliferative treatment; in another study, 40% of patients treated with MMC lost ≥2 lines of visual acuity (VA) and MMC group had worse outcomes than groups treated with 5-FU or controls; eyes treated with MMC had late hypotony and bleb leak; such adverse effects less frequent when broad treatment with MMC used (instead of focal application), but use of MMC still cause for concern.

Alternative treatments: tetrahydrocannabinol (THC) — for THC to be effective, patient must experience “high”; drug also lowers blood pressure, so may not have beneficial effect on optic nerve; THC not recommended for glaucoma; Ginkgo biloba — in crossover study, mean sensitivity and corrected pattern standard deviation improved while patients taking G biloba; but unclear whether drug has protective effect or short-term physiologic effect; findings do not imply that drug prevents progression of disease; more recent study evaluated 28 newly diagnosed patients and found that neither G biloba nor placebo affected short-term visual function; conclusions cannot be drawn regarding efficacy of G biloba; calcium channel blockers— older studies included plunging hands into cold buckets of ice to study capillary flow in model of cold-induced vasospasm; brivancicline centrally.

Educational Objectives

The goal of this program is to improve diagnosis and treatment of glaucoma. After hearing and assimilating this program, the clinician will be better able to:

1. Discuss targets for lowering intraocular pressure in patients with glaucoma in light of the findings of the Collaborative Normal Tension Glaucoma Study.
2. Rank alternative medical treatments for glaucoma based on the quality of available evidence.
3. Describe recently developed surgical devices for management of glaucoma.
4. Write a protocol for clinical evaluation of glaucoma suspects and patients with glaucoma.
5. Illustrate common findings in the optic discs of patients with glaucoma.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the following has been disclosed: Dr. Heuer is on the data and safety monitoring boards for Aeon Astron (Body Organ Biomedical Corp) and Innovia LLC. Dr. Stamper is a consultant for Transcend Medical, receives grant/research support from Aerie Pharmaceuticals, and is medical director of Sight Science (a NovaVision company). The planning committee reported nothing to disclose. In his lecture (“Management of Progressive Normal-tension Glaucoma”), Dr. Heuer presents information related to the off-label or investigational use of a therapy, product, or device. In his lecture, Dr. Stamper presents information related to the off-label or investigational use of a therapy, product, or device.
acting calcium channel blocker and vasodilator that showed benefit; treated patients had no change over 2 yr in mean defect, but modest decline observed in untreated group; no trend toward worsening observed at any point in bromocaine group; drug not available in United States, but these findings suggest that off-label use of calcium channel blockers may be reasonable; however, many patients with progressive normal-tension glaucoma already have low blood pressure and cannot be treated with calcium channel blockers; brimonidine — neuroprotective in rat crush model of optic nerve injury; efficacy in chronic glaucoma unknown; in Low-pressure Glaucoma Treatment Study (LoGTS), patients on brimonidine had similar reductions in IOP compared with other patients but had better outcomes; study suggests that β-agonists may protect ganglion cells

**Management:** evidence suggests progression related to IOP in many patients; reduction in pressure of 30% to 35% reasonable

**Diagnosis:** if diagnosis uncertain — additional testing or evaluation by neuroophthalmologist indicated if unclear that condition is nerve fiber bundle defect consistent with glaucoma, if pallor more pronounced than cupping, if nonretinal nerve bundle defects present, if cupping and visual field defects do not correlate, or if patient worsening even after IOP lowered to ≤10 mm Hg with filter; **findings associated with glaucoma** — study compared 29 patients with normal-pressure glaucoma who underwent diagnostic imaging and 28 consecutive controls with nonglaucomatous defects; patients with glaucoma tended to be older and had better VA, greater vertical loss of neuroretinal rim (at superior and inferior poles), more disc hemorrhages, less pallor of neuroretinal rim, and vertically aligned defects in nerve fiber bundle; good discriminators for glaucoma include vision worse than 20/40, vertically aligned visual field defects (test should be repeated), and pallor more severe than cupping; younger patients more likely to have issues other than glaucoma

**Suggested Reading**


**Glucoma**

Robert L. Stamper, MD, Distinguished Professor of Clinical Ophthalmology, University of California, San Francisco

**Minimally invasive procedures:** may be performed in conjunction with cataract surgery; objective to reduce dependence on medication and improve control of disease; most procedures claim to reduce IOP to midteens with few risks; therapies approved by Food and Drug Administration include Trabectome device, iStent trabecular micro-bypass system, TRAB360 device, and possibly (“through back door”) gonioscopy-assisted translimbal trabeculotomy (GATT); other therapies awaiting approval in next 1 to 3 yr

**Trabectome:** acts as miniature spark plug that propagates electrical charge across gap; ceramic plate fits into canal of Schlemm through trabecular meshwork; radiofrequency cautery used to ablate meshwork; Trabectome makes clean 1-mm opening in meshwork and theoretically does not harm outer wall of canal; rate of success 70% in >700 patients; effect durable at 4 yr; patients able to reduce number of medications

**TRAB360:** like Trabectome, involves ab interno trabeculotomy; nylon-like material threaded through canal of Schlemm for 180°; clean tear in trabecular meshwork created as instrument retracted from eye, effecting trabeculotomy; if desired, suture may be retracted and instrument turned to treat other 180° during same procedure; treatment associated with decreased IOP regardless of whether concomitant cataract surgery performed

**iStent:** snorkel-like stent placed in canal of Schlemm, bypassing trabecular meshwork; instrument inserted across anterior chamber, and canal threaded to allow placement of 1-mm titanium stent; bleeding confirms proper placement; in randomized trial, reduction in IOP slightly greater in patients treated with iStent plus cataract surgery compared with cataract surgery alone; mean IOP slightly different at 12 mo and no different at 24 mo; only marginally better than cataract surgery alone but has low rate of complications

**Alternatives to minimally invasive procedures:** cataract surgery plus filtration may result in hypotony; in most studies, 50% of patients treated this way obstructed within 1 yr

**Case:** 60-yr-old Japanese-American woman, teacher and lifetime myope; had 10-yr history of normal-tension, open-angle glaucoma but otherwise healthy; maximum IOP 23 mm Hg; visual field testing showed progression; patient allergic to brimonidine and brinzolamide and having increasing symptoms of glare; patient had cataract extraction with Trabectome in left eye; IOP 48 mm Hg on day 1; despite burping wound and topical treatment, IOP 46 mm Hg on day 2, 36 mm Hg on day 3, and 32 mm Hg on day 7; 1-mm hypHEMA and blood clot visible at site of procedure, blocking drainage and unresponsive to burping; IOP fell in second week; over next several weeks, oral carbonic anhydrate inhibitors discontinued; at 3 mo, IOP 15 mm Hg on maximum medical therapy; central VA increased to 20/25 but preexisting paracentral scotoma enlarged; other cases of increased IOP and worsening after minimally invasive procedures reported; iStent may not be best option for patients with significant damage to optic nerve

**Summary:** minimally invasive procedures for glaucoma not always benign; randomized trial underway to test new Rho kinase inhibitor; 1-yr study being conducted in patients with primary open-angle glaucoma or untreated ocular hypertension (IOP>24 mm Hg); medication to be compared with timolol

**Suggested Readings**


**Clinical Optic Disc Examination**

Dr. Heuer

**Overview:** ophthalmologist can identify discs at risk for glaucoma; in addition to immediate impression of optic nerve, more systematic evaluation should be performed; for patients with primary open-angle glaucoma and those with suspected glaucoma, American Academy of Ophthalmology (AAO) recommends clinical examination with magnified stereoscopic view and documentation of condition of nerve with color stereophotography or computer-based image analysis; image analysis has more support in literature (level II evidence) than clinical examination
Drs. Heuer and Stamper were recorded at the University of California, San Francisco, for their cooperation in the production of this issue.

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GLAUCOMA UPDATE

To test online, go to www.audiodigest.org and sign in to online services.
To submit a test form by mail or fax, complete Pretest section before listening and Posttest section after listening.

1. In the Collaborative Normal Tension Glaucoma Study, what percentage of patients worsened when intraocular pressure (IOP) was reduced by ≥30%?
   (A) 10%  (B) 20%  (C) 40%  (D) 60%

2. In a study evaluating latanoprost in patients with glaucoma that reported a mean diurnal reduction in IOP of 19%, reduction in IOP was most pronounced in:
   (A) Younger patients  (B) Women  (C) Patients with the highest IOPs at baseline  (D) Patients with the shortest duration of disease

3. In the Early Manifest Glaucoma Trial, patients treated with trabeculoplasty plus betaxolol showed:
   (A) Significant decreases in IOP  (B) No change in IOP  (C) Significant rates of adverse effects  (D) Similar rates of progression compared to controls

4. Which of the following treatments afforded neuroprotection against injury to the optic nerve in rat models?
   (A) Tetrahydrocannabinol  (B) Ginkgo biloba  (C) Brovincamine  (D) Brimonidine

5. Which device for treatment of glaucoma features a ceramic plate that fits into the canal of Schlemm?
   (A) Trabectome  (B) TRAB360  (C) iStent

6. A randomized study is being conducted in patients with primary open-angle glaucoma or untreated ocular hypertension to test a new Rho kinase inhibitor against:
   (A) Brinzolamide  (B) Brimonidine  (C) Timolol  (D) Surgical intervention

7. In patients with ocular hypertension, which of the following confers a 4-fold higher risk for glaucoma?
   (A) Small optic disc  (B) Notching of rim  (C) Disc hemorrhage  (D) β-zone of parapapillary atrophy

8. The Ocular Hypertension Study may have underestimated the risk for developing glaucoma in patients with ocular hypertension and disc hemorrhage because:
   (A) Patients with minimal ocular hypertension were excluded from the study  (B) Patients with disc hemorrhage at baseline were excluded from the study  (C) Few patients in the study developed disc hemorrhages  (D) Disc hemorrhages were not evaluated at every visit

9. A study conducted in the Netherlands reported increased risk for progression of glaucoma in patients with disc hemorrhage; what was the mean time from appearance of hemorrhage to progression of glaucoma?
   (A) 2 mo  (B) 6 mo  (C) 1 yr  (D) 3 yr

10. Hemorrhages of the optic disc in patients with glaucoma are most often found in which regions?
    1. Superotemporal
    2. Superonasal
    3. Inferotemporal
    4. Inferonasal
    (A) 1,2  (B) 1,3  (C) 2,3  (D) 3,4