Lessons Learned From Glaucoma Clinical Trials

Randomized clinical trials: trials with greatest influence on patient care include Ocular Hypertension Treatment Study (OHTS), Collaborative Normal Tension Glaucoma Study (CNTGS), Advanced Glaucoma Intervention Study (AGIS), and Tube Versus Trabeculotomy (TVT) study.

Ocular Hypertension Treatment Study: design — large, multicenter trial evaluated safety and efficacy of topical medications for preventing or delaying primary open-angle glaucoma (POAG) in patients with ocular hypertension (OH); >1600 patients randomized to observation vs topical therapy; objective to reduce intraocular pressure (IOP) by ≥20% and maintain IOP at <24 mm Hg; findings — mean reduction in IOP 22.5% in topical therapy group and 4% in observation group; cumulative probability of developing glaucoma more than twice as high in observation group, which demonstrated benefit of reducing IOP; diagnosis of glaucoma based on examination of optic nerve and/or visual field (VF) changes; risk factors associated with progression included older age, increased IOP, thin central corneal thickness (CCT), increased pattern standard deviation on VF, and increased cup-to-disc ratio; risk for progression significantly lower in patients with diabetes; when data from OHTS pooled with data from European Glaucoma Prevention Study, same risk factors predicted glaucoma but protective effect of diabetes not confirmed; OHTS demonstrated importance of repeating VF; cataract surgery associated with significant, sustained reduction in IOP; lessons from OHTS — lowering IOP in patients with OH reduces risk for POAG; however, not every patient with OH needs treatment; risk assessment may be used to identify patients at greatest risk; measurement of CCT standard of care in patients with OH; optic nerve should be examined to detect early glaucoma; change in VF should be confirmed; cataract surgery lowers IOP in patients with OH.

Collaborative Normal Tension Glaucoma Study: design — study investigated whether reducing IOP affects course of normal-tension glaucoma (NTG); study enrolled 230 patients with NTG; patients randomized to close observation vs treatment; objective to lower IOP by 30%; criteria for randomization progressive NTG based on VF or disc hemorrhage; findings — most patients achieved 30% reduction in IOP with medical therapy and laser trabeculoplasty; β-blockers and adrenergic agonists not allowed in study; protocol for judging progression of VF changed during study because progression overdiagnosed based on single examination; reducing IOP lowered risk for progression, but difference between groups not statistically significant until investigators controlled for effect of cataract; trabeculotomy may predispose to cataract, and cataract may affect VF; progression to glaucoma highly variable; some patients worsened quickly, whereas others remained stable throughout 7-yr study; risk factors associated with progressive NTG included female sex, non-Asian ethnicity, disc hemorrhage, and migraine headache; factors that predicted likelihood of benefit from treatment included lack of disc hemorrhage, female sex, family history of glaucoma, no family history of stroke, no personal history of cardiovascular disease, and no personal history of migraine; lessons from CNTGS — lowering IOP effective for NTG; significant reduction in IOP may be achieved through medical therapy and laser trabeculoplasty; trabeculotomy associated with development of cataract; cataract can confound interpretation of VF; multiple VF tests needed to confirm progression; course of disease variable; observation may be appropriate for early disease.

Advanced Glaucoma Intervention Study: design — patients with open-angle glaucoma on maximum medical therapy randomized to argon laser trabeculoplasty (ALT) followed by trabeculotomy vs trabeculotomy followed by ALT and repeat trabeculotomy; findings — in both black and white patients, trabeculotomy followed by ALT associated with significantly greater reduction in IOP; sustained decrease in VF defined as loss of 4 AGIS units; sustained VF impairment defined as AGIS score of 18 or worse; among black patients, no significant difference between treatment sequences in rate of sustained VF decrease or sustained VF impairment; among white patients, initial treatment with trabeculotomy associated with significantly lower risk for sustained VF decrease VF with trend toward lower rate of sustained VF impairment; sustained decrease in visual acuity (VA) defined as loss of ≥3 Snellen lines; sustained VA impairment defined as VA of 20/200 or worse; among black patients, treatment with trabeculotomy followed by ALT associated with significantly higher rate of sustained VA decrease (no significant difference in rate of sustained VA impairment observed between treatment groups); among white patients, no difference in rate of sustained VA decrease or rate of sustained VA impairment observed between treatment groups; based on these results, blacks should undergo laser trabeculoplasty whereas whites should undergo trabeculotomy; rate of cataract progression higher in group treated with trabeculotomy; failure of ALT or trabeculotomy associated with younger age and increased preoperative IOP; diabetes and postoperative complications associated with failure of trabeculotomy; in post hoc analysis, no progression of VF observed in patients with IOP <18 mm Hg at every visit; percentage of visits with IOP >18 mm Hg associated with progression, suggesting dose-dependent relationship between degree of IOP reduction and risk for progression; lessons from AGIS — reduction in IOP greater with trabeculotomy than with ALT; younger patients and patients with increased preoperative IOP at greater risk for failure of either treatment; diabetes and...
postoperative complications associated with failure of trabeculectomy; findings do not imply that IOP of every patient should be maintained at <12 mm Hg; AGIS data do not show that blacks do better than whites after laser trabecuoplasty, but rather that whites do better with trabeculectomy if procedure performed without antibiotic agent; mitomycin C (MMC) introduced since AGIS, which limits applicability of AGIS to clinical practice

TVT study: design included patients with previous ocular surgery (cataract surgery with lens implantation and/or failed filtering surgery); patients randomized to 350 Baerveldt implant vs trabeculectomy with MMC; findings — each procedure produced sustained reduction in IOP (to low teens); greater reduction in IOP achieved with trabeculectomy in first few months, but no difference observed between groups after 6 mo; each procedure reduced need for medical therapy, but mean number of glaucoma medications lower in trabeculectomy group during first 2 yr postoperatively; progressive increase in mean number of medications observed in trabeculectomy group, but tube group maintained stable level of medical therapy; at 2 yr postoperatively, no difference in number of medications used observed between groups; in survival analysis, cumulative probability of failure higher in trabeculectomy group; early postoperative complications more common after trabeculectomy, but many issues transient and self-limited; no significant difference in number of serious complications (requiring reoperation or resulting in loss of ≥2 lines of VA) and late complications between groups; no difference in VA changes between groups; lessons from TVT study — each procedure reduces IOP; favorable results with tube shunt in this study (as compared with previous studies) may reflect fact that study enrolled less refractory population; rate of surgical success higher with shunt than with trabeculectomy in patients with previous surgery; safety of both operations similar; tube shunt reasonable option in patients with previous surgery

Implications for management: β-blockers, α-agonists, and prostaglandin analogues not available when CNTGS conducted; such patients now treated with prostaglandin analogue, with β-blocker added as second agent; Low-Pressure Glaucoma Treatment Study suggested that brimonidine (Alphagan-P) beneficial in NTG, in addition to pressure-lowering effect of drug; CNTGS showed that IOP related to disease process in NTG; however, other factors also responsible for pathogenesis of NTG; even after correcting for effect of CCT on IOP, CCT remains independent predictor of development of glaucoma

Suggested Readings


Tube Shunts in the Surgical Management of Glaucoma

Function: tube shunts fluid to endplate and maintains patency of drainage fistula; endplate constructed from silicone or poly(methyl methacrylate), to which fibroblasts do not adhere; nonadherent capsule forms around device; aqueous humor pools in potential space between endplate and surrounding fibrous capsule, passes through capsule by passive diffusion, and undergoes absorption by pericellular capillaries and lymphatics; capsule site of major resistance to flow

Intraocular pressure: 2 major determinants of IOP after tube shunt surgery are thickness of capsule (thinner capsule correlates with lower postoperative IOP) and surface area of capsule (larger surface area correlated with lower IOP); randomized studies compared MMC with balanced salt solution (BSS; materials applied in region of endplate at time of implantation); no difference in thickness of capsule observed between groups; however, using endplate with larger surface area may produce lower IOP; randomized trial demonstrated greater reductions in IOP with double-plate Molteno implant than with single-plate device

Indications for tube shunts: expanding, traditionally reserved for eyes at high risk for failure with filtering surgery (eg, those with failed trabeculectomy or bleb scarring of conjunctiva); some conditions respond poorly to trabeculectomy (neovascular glaucoma, uveitic glaucoma, and glaucoma secondary to epithelial and fibrous downgrowth); child with previous failed surgery good candidate for shunt; aphakia requiring contact lens best treated with shunt rather than trabeculectomy (contact lens increases risk for bleb-related infection)

Nonvalved implants: Molteno and Baerveldt implants allow free flow of aqueous humor from tube to plate; Baerveldt 350 implant easy to insert and has larger surface area than double-plate Molteno implant; surgeon must temporarily restrict flow through nonvalved implant; patency and function of implant may be determined by looking for presence of bleb overlying endplate; when valve open and functioning, bleb forms

Valved implants: include Ahmed and Krupin valves; valve closes if IOP too low, so temporary restriction of flow not necessary; implant begins functioning immediately; single-plate Ahmed valve significantly smaller than Baerveldt 350 implant and produces less reduction in IOP

Surgical technique: limbus or fornix-based conjunctival flap used for insertion; implant usually in superotemporal quadrant, but any quadrant may be used; conjunctiva and Tenon capsule dissected away from sclera; clear corneal tracture suture improves exposure; endplate attached to sclera (measure with caliber to ensure device sufficiently posterior); Baerveldt implant placed under lateral and superior recti; endplate should not crowd insertion of muscle (this may cause dioplia); nonabsorbable suture such as 8-0 nylon used to attach endplate to sclera; flow should be restricted if implant nonvalved; tube ligated in water-tight fashion with 7-0 polyglactin
910 (Vicryl); suture dissolves in 5 to 6 wk as capsule forms; other techniques also may be used to temporarily restrict flow; tube trimmed to leave ≥2 mm segment in anterior chamber, with ante-rior bevel; 23g needle used to enter anterior chamber (tight inci-sion prevents leakage around tube); limbal portion of tube covered with patch graft; conjunctiva reapproximated to limbus; when suturing implant to sclera, knots should be rotated into eyelet so they do not erode through conjunctiva; BSS used to ensure that tube watertight; tube fenestration (making small slits proximal to ligature) helps control IOP until tube opens; subconjunctival injec-tion of antibiotic and steroid given at end of case

Complications: similar to those associated with trabeculectomy, but unique (associated with implantation of foreign body); improper direction of entry incision for tube—may damage cornea, iris, or lens; after inserting tube through needle tract, position of tube should be checked; tube may be removed and reinserted through new needle tract if position not optimal; scleral perforation—possible when fixating endplate; retinal cryotherapy indicated if vitre-ous lost; hyphema possible; intraoperative bleeding—should be irrigated; blood resorbs over time; hypotony—may occur in early postoperative period and may require ligation of tube; obstruction of tube—tube may become obstructed with blood, fibrin, iris, or vitreous; intracameral tissue plasminogen activa-tor can resolve obstruction due to fibrin or blood; laser treatment used for iris incarceration; vitrectomy usually required if vitre-ous obstructing tube; hypertensive phase—commonly observed after surgery; treated with aqeous suppressants; tends to resolve over time; after implantation of single-plate Molteno implant, hypertensive phase may occur with remodeling of capsule around endplate during wound healing; erosion of tube—may occur, usually few millimeters posterior to limbus; sewing conjunctiva over defect not effective; new patch graft required over area of exposure, and tube may need repositioning; tube too close to corneal endothelium—mechanical trauma to cornea may cause loss of endothelial cells and edema; best to reposition tube early; otherwise, keratoplasty may be necessary; diplopia—common in early postoperative period (especially with Baerveldt implant due to manipulation of muscles); usually improves as swelling and edema clear; however, some patients develop permanent strabismus, which may require removal of implant

Ongoing studies: multicenter trial now studying postoperative MMC injection after implantation of Ahmed valve; Ahmed valve may be more prone to develop thick capsule than non-valved implants because of inflammatory mediators present in aqueous just after surgery; in low-risk eyes with POAG and no previous ocular surgery, 80% of glaucoma specialists per-form trabeculectomy as initial procedure of choice, whereas 20% use aqueous shunt; Primary Tube Versus Trabeculectomy Study evaluating patients with POAG and other low-risk glau-coamas and no previous surgery; patients being randomized to Baerveldt 350 implant vs trabeculectomy with MMC

Suggested Readings

Acknowledgments
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1. Which of the following are findings of the Ocular Hypertension Treatment Study (OHTS)?
   1. No significant difference in intraocular pressure (IOP) was observed between observation and topical therapy groups
   2. A diagnosis of glaucoma was based on examination of the optic nerve and/or visual field (VF) changes
   3. Diabetes was associated with an increased risk for progression
   4. Older age was associated with an increased risk for progression
   5. Cataract surgery was associated with a significant, sustained reduction in IOP
      (A) 1,2,3 (B) 1,4,5 (C) 2,3,4 (D) 2,4,5 **

2. In the Collaborative Normal Tension Glaucoma Study (CNTGS), which of the following factors predicted the likelihood of benefiting from treatment?
   (A) Family history of glaucoma ** (C) Migraine headache
   (B) Male sex (D) Non-Asian ethnicity

3. In the Advanced Glaucoma Intervention Study (AGIS), reduction in IOP was significantly greater with trabeculectomy followed by argon laser trabeculoplasty (ALT) than with ALT followed by trabeculectomy in which of the following groups?
   (A) White patients (C) A and B **
   (B) Black patients (D) Neither A nor B

4. Which of the following is a conclusion of the AGIS?
   (A) Among white patients, rate of sustained visual acuity (VA) decrease was significantly greater with trabeculectomy followed by ALT than with ALT followed by trabeculectomy
   (B) Among white patients, rate of sustained VA impairment was significantly greater with trabeculectomy followed by ALT than with ALT followed by trabeculectomy
   (C) Among black patients, rate of sustained VA decrease was significantly greater with trabeculectomy followed by ALT than with ALT followed by trabeculectomy **
   (D) Among black patients, rate of sustained VA impairment was significantly greater with trabeculectomy followed by ALT than with ALT followed by trabeculectomy

5. In the AGIS, all the following factors were associated with a greater risk for failure of trabeculectomy, EXCEPT:
   (A) Older age ** (C) Diabetes
   (B) Postoperative complications (D) Increased preoperative IOP

6. Application of AGIS findings to clinical practice is limited because:
   (A) Patients were not randomized within ethnic groups
   (B) Mitomycin C (MMC) had not yet been introduced into practice **
   (C) Patients were already on maximal medical therapy
   (D) Progression of VF was not followed

7. Compared with a 350 mm² Baerveldt implant, trabeculectomy with MMC was associated with which of the following in the Tube Versus Trabeculectomy study?
   (A) Fewer medications during the first 2 yr **
   (B) Fewer medications after the first 2 yr
   (C) Lower cumulative probability of surgical failure
   (D) Increased number of serious postoperative complications

8. The 2 major determinants of IOP after tube shunt surgery are:
   (A) Number of plates in device and thickness of capsule
   (B) Presence of valve in device and thickness of capsule
   (C) Surface area of capsule and thickness of capsule **
   (D) Location of surgical flap and number of plates in device

9. To confirm the function and patency of the valve in a glaucoma implant, the surgeon should do which of the following?
   (A) Calibrate the device using the manufacturer’s directions
   (B) Chart successive IOP measurements
   (C) Confirm pooling near the shunt using ultrasonography
   (D) Look for a bleb overlying the endplate

10. If a hypertensive phase is observed after glaucoma implant surgery, the surgeon should do which of the following?
    (A) Reposition the tube
    (B) Prescribe an aqueous suppressant
    (C) Use tissue plasminogen activator
    (D) Remove the implant