Glaucoma in the New Millennium

Practitioners had assimilated the innovations of the 1990s and anticipated an era of neuroprotection and bleb-free surgery.

BY RICHARD A. LEHRER, MD

Was the year 2000 among the good old days? It is difficult for me to remember, especially when it comes to my practice. I had been out of fellowship for 7 years, and my practice had become extremely busy. For me, it seems useful to discuss several areas of practice: the office and medical care of patients, research, and the surgical care of patients.

MEDICAL THERAPY

We physicians had several new medications to use. After 4 years’ experience with the drug, we were using latanoprost (Xalatan; Pfizer Inc.) as first-line therapy. Unoprostone (Rescula; Novartis Ophthalmics, Inc.), another prostaglandin analogue, was introduced that year, and many of us were gaining clinical experience with it. The fixed combination of dorzolamide and timolol (Cosopt; Merck & Co., Inc.) was in wide use, and there was a great deal of buzz concerning brimonidine (Alphagan; Allergan, Inc.) and the possibility of neuroprotection. Animal studies in this area seemed to be quite promising.

The introduction of each new medication brought short-term reductions in glaucoma surgery, as we hoped these agents would preclude the need for surgery. Many of us were also trying to find a niche for all of the β-blocker drops. Alas, medical therapy usually just delayed surgery.

RESEARCH

The seventh report from the Advanced Glaucoma Intervention Study (AGIS)¹ provided strong evidence that low pressures were useful in preserving vision in advanced glaucoma. Many of us who were already adopting lower target pressures for more severe glaucoma now felt justified in lowering them even further.

SURGERY

The availability of small, portable diode lasers at 810 nm made it easier for those of us with satellite offices to provide laser trabeculoplasty at each location. These units were also useful for suture lysis after trabeculectomy. The Nd:YAG laser for selective laser trabeculoplasty had been recently introduced and was showing promise, although it was not yet available in the United States.

Surgically, 2000 was an interesting time for me, especially in regard to nonpenetrating glaucoma procedures. Many of us, myself included, were tired of managing the bleb-related complications of trabeculectomy, and the promise of surgeries that did not depend on a bleb and perhaps had fewer complications was extremely attractive. I had been performing viscocanalostomy for about 2 years and was often a little disappointed with the intermediate-term results. I found a good deal of anecdotal evidence from European researchers like Philippe Sourdille, MD, and André Mermoud, MD—which was later backed by studies—that combining a spacer device such as the AquaFlow Collagen Drainage Device (STAAR Surgical Company, Monrovia, CA) with mitomycin C (MMC) could greatly improve the long-term success of nonpenetrating deep sclerectomy.

These were not blebless surgeries, but usually the bleb was posterior, low lying, and thicker than those of trabeculectomy with MMC. Complication rates (both short- and long-term) seemed lower, with fewer cases of hypotony-related complications like choroidal effusions and flat chambers as well as fewer bleb leaks. The procedure was somewhat more technically demanding than trabeculectomy,² especially in terms of the creation of a trabeculo-Descemet’s window and peeling the deep layer of Schlemm’s canal.

In addition, nonpenetrating deep sclerectomy had a few unique complications, including fibrosis of the trabeculo-Descemet’s window with a loss of permeability and increased IOP. The remedy was also unique: the use of Nd:YAG gonipuncture. Another complication not usual in trabeculectomy was incarceration of the iris in the trabeculo-Descemet’s window, since a peripheral iridotomy was not routine. This problem could sometimes be solved with laser goniplasty, iridoplasty, and iridotomy.

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Other cases required a trip to the OR to reduce the incarceration and perform a surgical iridotomy. Fortunately, I achieved long-term success with this procedure, and many of these eyes still have functioning blebs.

CONCLUSION

In the subsequent decade, more prostaglandin analogues have come on the market, and we clinicians have moved away from and back to β-blockers, other fixed-combination agents, and a plethora of generics. My office staff is now constantly hounded by managed care plans to persuade me to change my patients’ medications. Neuroprotection in humans remains elusive. In my practice, selective laser trabeculoplasty has supplanted argon and diode laser trabeculoplasty. Canaloplasty with suture tensioning has replaced deep sclerectomy as my non-penetrating surgery of choice, again with the promise of a blebless procedure. Many of us are striving for a better surgical alternative for lowering IOP.

The good old days were not in 2000 for me, but in many ways, this year was evolutionary with regard to the practice of glaucoma.

This article discusses off-label uses of medications.

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BY LISA F. ROSENBERG, MD

As the 21st century began, physicians availed themselves of a wide variety of diagnostic tests and a growing arsenal of topical glaucoma therapies.

DIAGNOSTICS

With the millennium came a new paradigm in the characterization of the optic nerve. Although stereo disc photography remained the gold standard, automated optic nerve analyzers became widely used in clinical practice. With the aim of earlier detection of glaucomatous optic neuropathy, three techniques emerged: scanning laser polarimetry (GDx; Carl Zeiss Meditec, Inc., Dublin, CA), confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph; Heidelberg Engineering GmbH, Heidelberg, Germany), and optical coherence tomography (Stratus OCT; Carl Zeiss Meditec, Inc.). The ability to accurately, objectively, and quantitatively measure the optic nerve was innovative and extraordinarily appealing. Patients and ophthalmologists alike were intrigued by this concept, which wowed both groups with snazzy, three-dimensional, color images created in a few seconds. These devices held the promise of becoming an essential and complementary element of glaucoma care, even if their long-term role was yet to be established.

Two visual field strategies became available for clinical use. By testing a sparse and less redundant system of ganglion cells with blue light on a yellow background, short-wavelength automated perimetry allowed ophthalmologists to demonstrate early functional loss sooner than standard white-on-white perimetry. This method of testing proved powerful in high-risk patients with clear media. Frequency-doubling perimetry presented a frequency-doubled illusion at a low spatial frequency sinusoidal grating thought to measure the function of a subset of ganglion cells different from those assessed with short-wavelength automated perimetry. Because of its high correlation with glaucomatous defects measured by standard perimetry, the utility of frequency-doubling perimetry lay in its short testing time and its ease of use for screening. Glaucoma specialists now had more than one strategy by which to characterize functional ocular deficits.

PHARMACEUTICALS

The popularity of miotics and oral carbonic anhydrase inhibitors was falling, as myriad new and effective topical therapies became available. Most notably, latanoprost (Xalatan; Pfizer Inc.), which had been approved for use in 1996, was joined by bimatoprost (Lumigan; Allergan, Inc.) and travoprost (Travatan; Alcon Laboratories, Inc.). This class of drugs was not only extremely effective at lowering IOP, but it also offered a practical dosing schedule for patients who had a track record of poor adherence to prescribed therapy.

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—Lisa F. Rosenberg, MD
Nevertheless, 10 years ago, timolol was still the first-line drug of choice, and prostaglandins were relegated to third- or fourth-line therapy. Concerns over iris pigmentation and ocular redness deterred some patients from using prostaglandin analogues. These agents demanded extra “chair time” from ophthalmologists in order to explain their side effects and field patients’ phone calls about red, irritated eyes.

Other new therapeutic options at the time included the first fixed combination of dorzolamide and timolol (Cosopt; Merck & Co., Inc.) and a new formulation of the \(\alpha\)-adrenergic brimonidine-Purite 0.15% (Alphagan; Allergan, Inc.) designed to reduce ocular allergy. Generic medications were becoming available. Their efficacy was questioned by some clinicians, however, and these agents did not gain a significant market share.

The holy grail of neuroprotection became a big topic at clinical meetings. Evidence that neuroprotection might play a role in glaucoma therapy could be found in cell culture and animal models of optic nerve injury and ischemia, which demonstrated that the death of retinal ganglion cells could be prevented by specific pharmacologic agents.\(^1\) Toward this end, the multicenter, randomized, clinical investigation of memantine was initiated. A multicenter, prospective, randomized trial was already underway to determine if brimonidine 0.2% had a neuroprotective effect independent of IOP in patients with normal-tension glaucoma.

**TREATMENT ALGORITHM**

With so many possible therapeutic combinations, the definition of maximal medical therapy was debated at meetings. The selective laser was not yet an option for trabeculoplasty, so argon laser trabeculoplasty was kicked down the treatment algorithm after medical management failed to adequately control IOP. As a result, less laser and incisional surgery was being performed nationwide.

Trabeculectomy, with or without antifibrotic therapy and releasable sutures, and seton surgery were established modes of surgical treatment at the turn of the millennium. In response to the continuing search for a surgical procedure with improved efficacy and reduced complications, the concept of nonpenetrating surgery was introduced in the form of viscocanalostomy. It was embraced by comparatively few ophthalmologists. Most glaucoma surgeons remained a conservative bunch and greeted this technique with skepticism.

**CONCLUSION**

Overarching challenges in glaucoma remain lightening rods for research and clinical care regardless of the decade. Where does the site of outflow resistance reside in glaucoma? What damages the optic nerve? What is the best initial surgery for glaucoma? How is functional progression best detected? How is structural change best detected? Clinicians are fortunate to work in a dynamic field where the management of and cure for glaucoma are lofty and challenging pursuits but ones that are thoroughly fulfilling.

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**BY WILLIAM ERIC SPONSEL, MD**

What a year 2001 was! We physicians were definitely a part of the big new wave; we were not necessarily riding its very crest, but we were not watching from the shoreline, either. I think it fair to say that those of us involved in clinical practice were bravely bodysurfing the myriad Y2K tidal changes. The fact that clinical practice a decade ago was in many ways similar to how it is today is more a reflection of the rapid changes that immediately preceded the year 2000 than undue stagnancy since.

**DIAGNOSTIC TECHNOLOGY**

Major epidemiologic studies revealed the stunning reality that normal-tension glaucoma comprised the major proportion of all open-angle glaucoma sufferers worldwide.\(^1\) On cue, the new millennium brought us the necessary means to diagnose glaucoma in everyone, regardless of the presence or absence of ocular hypertension. The ingenious innovation of Ted Madess, PhD, the frequency-doubling perimeter was commercially developed by Welch Allyn Medical Products (Skaneateles Falls, NY) and wisely acquired by Carl Zeiss Meditec, Inc. (Dublin, CA). The frequency-doubling perimeter provided previously unheard of levels of diagnostic sensitivity and specificity. The device was promptly officially recognized by Prevent Blindness America’s Glaucoma Committee and adopted by the Congressional Glaucoma Caucus, which initiated a new era in glaucoma screening.

Early glaucoma detection and structural monitoring took off in 2000 as well, as reflected in an influential
article by Linda Zangwill, PhD, and colleagues that compared the HRT (Heidelberg Engineering GmbH, Heidelberg, Germany), GDX (Carl Zeiss Meditec, Inc.), and optical coherence tomographer (Carl Zeiss Meditec, Inc.). These technologies were newly in clinical use by then, and nerve fiber layer imaging has become a mainstay of modern clinical practice.

**SURGERY**

All of the current forms of laser therapy were widely used except for selective laser trabeculoplasty. Mito-mycin C was supplanting 5-fluorouracil as the favored antifibrotic agent, and the nonpenetrating procedures introduced by Thom Zimmerman, MD, PhD, and popularized by André Mermoud, MD, were gaining worldwide acceptance. The pioneers of viscocanalostomy were already hard at work, and almost all subspecialists had replaced top hat scleral tunnel combined procedures outflow without regard to episcleral venous pressure.

Tube shunts had evolved into high-quality implants very similar to those currently available. Tutoplast (IOP Inc., Costa Mesa, CA) and eye-banked sclera were both acceptable options for reinforcement grafts.

This difference opened up the possibility of treating a huge new cadre of patients, including those with nonmotensive open-angle glaucoma. The approval of the first combination agent, Cosopt (timolol and dorzolamide; Merck & Co., Inc.), provided us with another eye drop that had potency commensurate with and additive to that of the prostanoids.

Still, we wanted more. Clinical and laboratory studies had made us aware of the potentially positive vasoactive effects of the carbonic anhydrase inhibitors and neuroprotective benefits of the α-agonists and β-blockers (betaxolol in particular). We naturally had high hopes of new vasoactive and neuroprotective agents that would help us contend with all the nonhydrostatic predisposing factors for open-angle glaucoma. No glaucoma drug had (or has) ever attained FDA approval by demonstrating a benefit in terms of visual function or neural structure. Who would have believed then that we would still be waiting?

**CONCLUSION**

Here is to the strong and brave new glaucoma generation! May they have the will to grab their boards and ride high above the aqueous surf to give future generations effective new therapeutic agents that modulate the full spectrum of factors underlying chronic glaucoma. In so doing, may these physicians and researchers lead the way toward better treatments for Alzheimer disease, Parkinson disease, and other debilitating neuro-ropathies! Cowabunga! ❑

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