Evaluating New Refractive Surgical Procedures: Free Market Madness Versus Regulatory Rigor Mortis

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In the past 10 years, numerous refractive surgical procedures have risen to levels of transient popularity, only to disappear quietly with few publications stating why they were abandoned. The urge to use the latest surgical technique is particularly strong in refractive surgery because development is rapid, surgeons want to offer patients the most current advantages, there is a prevalent attitude of hype, competition is intense to gain professional leadership, and the economic stakes are high for both practitioners and industry. These factors push unproven techniques into clinical use before their advantages and disadvantages are well defined, creating a pattern of free market madness that is unhealthy for refractive surgeons and patients. Let's examine it.

THE PATTERN

A new idea for a refractive surgical procedure emerges: sometimes as a modification of previous procedures (for example, hexagonal keratotomy), sometimes by serendipity (eg, deep lamellar keratotomy for hyperopia [hyperopic ALK]), sometimes as a technological improvement in a preexisting device (eg, phakic anterior chamber intraocular lenses), and sometimes as a new idea stemming from previous work (eg, epikeratoplasty).

Surgeons, often dubbed pioneers, enthusiastically describe this important advance at meetings, in ophthalmic newspapers, and in quickly prepared, colloquial books. Enamored of the idea, other surgeons learn to do the procedure and report their positive experience often based on informal data from nonconsecutive cases.

If the procedure is linked to new instrumentation, commercial firms promulgate the instruments and courses, usually brief 1- to 2-day seminars, taught by surgeon-consultants, some with recognizable reputations and others aspiring to build same.

The combined momentum of uncritical newspaper reporting, commercial advertising, positive spin by perceived experts, and articles in the literature with positive results creates a wave of popularity that surges forward, washing an increasing number of surgeons and patients with it. Sometimes the popularity is sustained simply because "We have no other procedure for that refractive disorder." However, a quiet undertow also develops as complications appear. Initially, the complications are given little public attention, for fear of lawsuits against the surgeon, to avoid tarnishing the growing reputation of the new procedure, or because of lack of understanding of the complications by practitioners, who sometimes behave like the crowd that extolled the beauty of the emperor's new clothes.

Finally, the procedure quietly disappears, sometimes because publications detail less-than-satisfactory results or a spate of complications, but more commonly because of unsatisfactory personal experience. Seldom do surgeons publish articles that detail their negative experiences and reasons for abandoning the technique.

Many refractive procedures have passed through this pattern. Let's look at three.

SPECIFIC EXAMPLES

Hexagonal Keratotomy for Hyperopia

Probably the most infamous was hexagonal keratotomy, a procedure that proves the adage, "Those ignorant of history are doomed to repeat it." Hexagonal keratotomy was first done by Sato and Akiyama in the early 1950s. In rabbits, the authors found a steepening of the central cornea, but observed variable results and the induction of large amounts of astigmatism, concluding it was an undesirable technique. Mendez revived it in Mexico in 1983, using intersecting incisions and a 6-mm diameter zone, and it attracted attention in the United States.

The wound healing problems of the intersecting incisions (which were already well known from the intersecting "T" incisions of Fyodorov and the intersecting trapezoidal incisions of Ruiz) led to the use of...
nonintersecting incisions by Mendez and Jensen. Because this pattern induced astigmatism, surgeons added transverse incisions outside the hexagon (the T-hex operation), which caused irregular astigmatism in many eyes. Casebeer reported results in 46 eyes, vaguely alluding to the irregular astigmatism as an increase in corneal asphericity, observing that hexagonal keratotomy was in the stage of trial and error refinement and informal testing. In spite of these problems and continued modifications, the Casebeer-Chiron courses on refractive surgery taught hexagonal keratotomy to hundreds of ophthalmologists.

Nordan and Maxwell published letters to the editor contending that hexagonal keratotomy should be abandoned because it induced irregular astigmatism and reduced quality of vision. Basuk and colleagues (but none of hex's enthusiastic practitioners) documented complications. Most surgeons have stopped doing hexagonal keratotomy—but only after a few thousand patients had received it, many with poor results.

Myopic Epikeratoplasty

This modification of keratomileusis, which used cryolathed, lyophilized tissue as an onlay graft, was popularized by Kaufman and McDonald with the support of Allergan Medical Optics. It is a good example of a procedure promulgated in numerous courses even though the surgical techniques were changing frequently. One unique feature of the nationwide trial was that most of the 116 investigators each contributed a small number of cases, making the trial a "worst case" study of a learning curve. Early results for myopia and modifications of the technique were reported, but the procedure proved unpredictable and unstable because of the bending of the epikeratoplasty lenticule. The procedure fell under the auspices of the FDA; AMO stopped making the lenticules, and most surgeons abandoned it, without publication of the follow-up results and complications.

Automated Lamellar Keratoplasty

Discussing ALK presents a more complex challenge, because many refractive surgeons still use it. Keratomileusis in situ (alias, ALK), in which a plano disc or flap of tissue is removed from the anterior cornea and the refractive cut is made with a micromere in the bed of the cornea, was popularized by Ruiz as a method of expanding the range of myopic correction and of simplifying the keratomileusis procedure. Although the technique has been shown to reduce a wide range of myopia, it suffers from two fundamental flaws: (1) The refractive cut is a plano excision of tissue made with an instrument that has an accuracy of only 10 to 20 µm, producing less than desirable predictability and frequently requiring repeated surgical enhancement. (2) The diameter of the refractive cut is approximately 4.5 mm, placing the inflection zone of corneal curvature within the normal pupil under dim light conditions and creating optical aberrations. Nevertheless, the technique was imported to the United States and propagated widely in courses by Slade and Casebeer with Chiron Vision sponsorship before publication of results.

ALK has contributed to our knowledge of lamellar refractive surgery and has paved the way for excimer laser in-situ keratomileusis (LASIK), in which the refractive cut is spherocylindrical and the diameter of the refractive ablation is 6.0 mm or more. Even though LASIK is more expensive and technologically more complex than ALK, I think its spherocylindrical ablation center, larger diameter, greater surgical simplicity and better predictability will cause it to replace ALK, an opinion that requires the proof of published results. In fact, I wonder whether surgeons should continue to do ALK at all.

ALK spawned surgical aberration, capless ALK, propagated by Hollis after he observed that when a cap was lost, the corneal bed reepithelialized and the eye retained a refractive change. He reasoned that this approach was not completely different from excimer laser photorefractive keratotomy. Capless ALK was short-lived because it caused irregular astigmatism and corneal scarring in some eyes.

More Examples

Other procedures have been done in hundreds or thousands of eyes, before problems were detected:
- Connected trapezoidal keratotomy for astigmatism with the complication of poor corneal wound healing.
- High-vaulted Baikoff phakic anterior chamber intraocular lenses for myopia with the complication of endothelial cell damage.
- Deep lamellar keratotomy for hyperopia (hyperopic ALK) with the complication of corneal ectasia when the incision was more than approximately 70% deep.
- Excimer laser photorefractive keratotomy with a 4.5-mm diameter ablation zone for myopia greater than 10.00 D with the complications of corneal scarring and regression of effect.
- Hot needle radial thermokeratoplasty of Eyodorov with the complication of induced irregular astigmatism and regression of effect.
- Radial keratotomy with small diameter clear zones with the complication of irregular astigmatism.

PROBLEMS WITH THE AGGRESSIVE MARKET APPROACH

All of the above procedures have increased our knowledge of refractive surgery but I think the clinical morbidity has been too great, as a result of free market madness and its fundamental flaws:

1. The interests of surgeons are put before the interests of patients.
2. Too many procedures are done on too many patients before the risks and benefits are well defined.

3. The surgeon's true belief that each technique is a real advance reduces his or her ability to see and report complications and then to document the reasons that the procedure was stopped or changed.

4. There is inadequate collection and reporting of early clinical data.

**REGULATORY RIGOR MORTIS**

At the other end of the spectrum is regulatory rigor mortis, where surgeons and patients face inordinate delays by government regulatory bodies in the approval of devices used in refractive procedures. Delays in objective assessment of new procedures are sometimes prolonged by mindless resistance to innovation and change by overly conservative ophthalmic organizations and practitioners. Few would dispute that the US Food and Drug Administration provides needed protection for refractive surgery patients. The problem is the long time and the high cost required for approval of devices, such as the excimer laser for photorefractive keratectomy.

An example from the development of intraocular lenses for cataract surgery illustrates the important role of regulation. When closed loop anterior chamber IOLs were being tested, the FDA had approved a core investigation of 500 eyes for each of the Azar, Surgidev, Leiske, Hessberg, and other styles. Had the number of eyes investigated remained at this level, the complications from these lenses (fibrosis of the loops in the angle, corneal edema, and in some eyes the uveitis-glaucoma-hemorrhage syndrome) would have occurred in a limited number of patients. However, in an attempt to meet the demands of surgeons and patients for the latest IOL technology, the FDA allowed the adjunct use of closed loop IOLs, which required minimal reporting. Free market madness emerged and hundreds of thousands of “adjunct” lenses were implanted that led to another peak in the 50-year epidemic of pseudophakic corneal edema before the lenses were removed from the market.

In terms of refractive surgery, the FDA faces the challenge of establishing guidance protocols, standards for investigation, and criteria for safe and effective outcomes. For excimer laser photorefractive keratectomy, the three-phase investigational protocol has required approximately 8 years for companies to complete. Developing outcomes criteria has further delayed approval and created the feeling of regulatory rigor mortis among US ophthalmologists.

The FDA could decrease the time and expense of such trials by establishing specific “bare minimum” guidelines that cover the major variables of refraction, visual acuity, and complications. Limited substudies could then be done on the more expensive and complex tasks—especially those that do not have well-accepted outcome standards—such as contrast sensitivity testing, glare testing, corneal topography, and endothelial specular microscopy. The current requirements for comprehensive prolonged testing on all patients discourage manufacturers from entering the field with new innovations, increase health care costs, exhaust investigators, erode the consistency of patient follow up, and ultimately slow the release of products in the United States.

**PROPOSALS FOR MORE RATIONAL EVALUATION**

How can refractive surgeons and commercial firms most responsibly introduce and evaluate new refractive surgical procedures, encourage innovation and early adaptors, and at the same time prevent complications in large numbers of patients? Consider 10 idealistic proposals:

1. Strive to maintain an attitude of professional restraint that honestly and compassionately minimizes risks for patients. Bona fide oversight by an institutional review board can help surgeons investigate new ideas.

2. Resist the professional and business pressures that create a mindless rush to be the first doctor with the latest procedure in the most patients for the greatest profit.

3. Evaluate new techniques by uniform international standards. Stating “He has done hundreds of cases and the results are great; he just doesn’t publish much” is inadequate.

4. Retain critical discussion of papers presented at meetings to challenge unsupported conclusions and to expose biased claims.

5. Couple a staged evaluation of new techniques with accurate reporting of the results in consecutive series of eyes using a Phase I, II, III paradigm to solve problems and change techniques initially in a small number of eyes.

Phase I—Initial determination of basic effectiveness and safety at one or two locations on a small number of eyes (eg, 10 to 20) with 3 to 6 months follow up.

Phase II—Refinement of techniques and devices at multiple locations (eg, 5 or 6) in a larger number of patients (eg, 100) with approximately 6 months follow up. This is usually done by colleagues or the originator or by surgeons selected by manufacturers.

Phase III—Determination of effectiveness and safety at multiple sites (eg, 10 to 20) on a few hundred patients (eg, 500 to 1000) followed for 1 year or more. The specific numbers can be altered for each procedure, but this gradual approach with its requisite reporting of results and independent peer review
seems appropriately protective of patients, appropriately graded for clinical development by investigators, and appropriately staged for technical development by commercial firms.

6. Establish guidelines for conducting clinical trials in refractive surgery through the International Society of Refractive Surgery (ISRS) and other concerned organizations, as has been done for treatments of lacrimal dysfunction by participants in a National Eye Institute Workshop. Standards for reporting refractive surgical procedures have been published in this Journal. The FDA held hearings to establish outcome standards for laser corneal surgery on July 20, 1995.

7. Disclose the weaknesses and drawbacks of a technique while extolling its virtues and advantages, so that more impressionable colleagues will have a balanced view and a cautious approach. During development, evaluate it; don’t sell it.

8. Publish and present papers and developments to actively inform the profession and the patients of new innovation; peer-reviewed journals will publish letters to the editor, brief reports, case studies, preliminary results, in addition to detailed original articles.

9. Avoid premature teaching of evolving and unproven procedures to hundreds of surgeons who may operate on tens of thousands of patients before discovering important changes or complications.

10. Publish negative results and evidence why a technique should be or has been abandoned to minimize repetition of the same problems. This process, similar to postmarket surveillance, may last for years, as occurred with documentation of the hyperopic shift after radial keratotomy.

Many surgeons and companies are developing new refractive surgery techniques in the general spirit of these precepts, although they have not completely escaped the influences of premarket madness and regulatory rigor mortis:

- Intracorneal ring for myopia
- Holmium:YAG thermokeratoplasty (see the article by Armausu and colleagues on page 358 in this issue)
- The prospective trial of the Casebeer/Chiron system of radial and transverse keratotomy
- The FDA trials of excimer laser photorefractive keratectomy and LASIK in the United States
- Nd:YAG and Nd:YSGG laser intrastromal photodisruption
- Intracorneal lens for presbyopia
- Iris claw and posterior plate myopia intracorneal lenses (see brief report by Erturk on page 388 in this issue).

Vigorous investigation and honest disclosure of results coupled with personal restraint and a patient-as-partner philosophy allow us to evaluate new refractive surgery procedures without succumbing to either free market madness or regulatory rigor mortis.

REFERENCES

The Challenge of Corneal Wound Healing After Excimer Laser Refractive Corneal Surgery

Three articles in this issue emphasize that subepithelial stromal corneal wound healing affects the amount of corneal haze and the refractive outcome after photorefractive keratectomy for myopia. Durrie and colleagues describe the spectrum of spectral wound healing responses, aggressive healing being associated with increased haze and a myopic refractive shift, and inadequate healing being associated with a persistently clear cornea and residual hyperopia. Grimm and colleagues describe regional variations in stromal wound healing within the ablation zone, areas of haze being associated with steeper corneal curvature and clear areas being associated with flatter corneal curvature. Corbett and colleagues review the basics of corneal wound healing and the role of topical corticosteroids in its modulation. (Epithelial wound healing probably plays a role in the refractive outcome, hyperplasia being associated with a loss of the initial refractive effect, but there is currently no practical clinical method for measuring epithelial thickness.) This variability in corneal wound healing may be affected before surgery, during surgery, and after surgery. How can the surgeon control these factors to increase the predictability of refractive outcome and the uniformity of corneal clarity and curvature? Let’s examine a few of these factors.

FACTORS BEFORE SURGERY

Before surgery, the energy distribution in the laser beam may be variable, giving variable impact on the cornea that could stimulate variable wound healing. Hot spots in the beam give greater ablation. Before surgery, manufacturers must develop methods to accurately measure the pulse energy and beam energy distribution of the excimer laser—methods that can be used immediately before treatment to control the symmetry of radiation exposure. This technology is in evolution. Manufacturers currently provide test materials (which must be accurately made and calibrated themselves) to quantify the pulse energy, determining the number of pulses needed to penetrate or shape the material. Beam quality and energy distribution are more difficult to measure and usually require special techniques, such as profilometry of ablated plastic surfaces; because the testing is performed by the manufacturer, it is not practical to use before treating each patient. Gottsch and colleagues have described a practical method of clinically measuring energy distribution over the laser beam using digital imaging of ablated test materials. Beam uniformity is a very important factor in large area ablations with a single laser beam (eg, Summit, VISX, Chiron) but may be less important in systems that use a smaller scanning beam (eg, Nidek, Meditec, Novatec) where hot spots and cold spots can overlap and create more uniformity. Until excimer laser beams can be calibrated reliably before each procedure, as is commonly done in radiation therapy of neoplasms, the surgeon will have a difficult time determining the effect of variations in beam quality on corneal wound healing.

FACTORS DURING SURGERY

During surgery, variations in epithelial removal, corneal hydration or patient movement, may distribute the energy unevenly in the stroma, resulting in variable wound healing. Mechanical removal of the corneal epithelium must be uniform and gentle to avoid damage to Bowman’s layer. The surgeon who uses either a gentle brushing or whisking motion with a blade or a soft rotating brush will accomplish this better than a surgeon who roughly scrapes off the epithelium. Because the epithelium is not uniformly