

Minimally Invasive Vitreoretinal Surgery Is Sutureless Vitrectomy the Future of Vitreoretinal Surgery?

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PRO

Introduction

Pars plana vitrectomy (PPV) was introduced almost 40 years ago.¹ In the 1980s and 1990s, three-port PPV with 20-gauge (G) instruments was the norm. In 2002, 25-gauge transconjunctival sutureless vitrectomy (TSV) was introduced.^{2,3} This system permits three-port PPV using microcannulas, trocars, and 25-G instrumentation without requiring sutures to close the sclerotomies. Subsequently, a similar technique but with 23-G instruments was developed.⁴ Currently, 25- and 23-gauge systems constitute the two most popular TSV techniques.

Herein, we review the advantages and disadvantages of small-gauge vitreous surgery.

Instrumentation

TSV consists of a 23-G or 25-G microcannular system and a wide array of vitreoretinal instruments specifically designed for this operating system. The microcannula consists of a thin-walled tube, 4 mm in length. A collar is present at the extraocular portion, which can be grasped with a forceps to manipulate the microcannula. The insertion trocar has a sharp tip that forms a continuous bevel with the microcannula, allowing easy entry through the conjunctiva into the eye (Fig. 1). The 25-G infusion cannula consists of a small tube that fits neatly and can be directly inserted into the cannula in the inferotemporal quadrant.

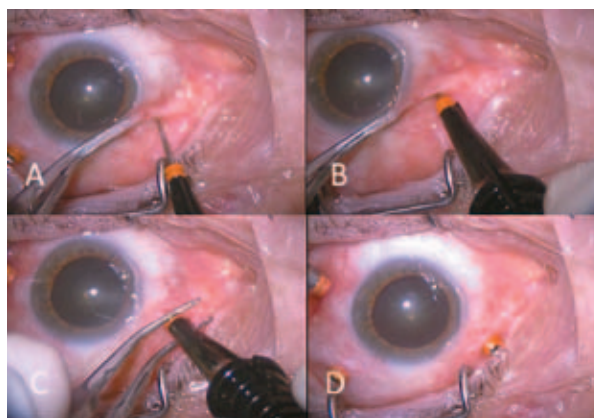


Figure 1. Insertion of 23-gauge trocars and microcannulas. The microcannulas are inserted through the conjunctiva into the eye by means of a trocar. Insertion is accomplished by first displacing the conjunctiva laterally by approximately 2 mm. An initially oblique, then perpendicular tunnel is made parallel to the limbus through the conjunctiva and sclera, thus creating a self-sealing wound.

A wide array of vitreoretinal microsurgical instruments complying with 25-G standards has been designed. These include vitreous cutters, illumination probes, intraocular forceps, microvitreoretinal blades, tissue manipulators, aspirating picks, aspirators, soft-tip cannulas, curved scissors, extendable curved picks, intraocular laser probes, and diathermy probes.

Surgical Technique

Small gauge vitrectomy is usually performed with the patient under local anesthesia. General anesthesia is only performed in

selected cases (children or uncooperative adults). After appropriate anesthesia, the operative field is prepared using antiseptic solutions. Preoperatively, the eyelash margins are scrubbed with povidone-iodine solution. The microcannulas are inserted through the conjunctiva into the eye by means of a trocar. Insertion is accomplished by first displacing the conjunctiva laterally by approximately 2 mm. An initially oblique, then perpendicular tunnel is made parallel to the limbus through the conjunctiva and sclera creating a self-sealing wound (Fig. 1). After insertion of the first microcannula, the intraocular portion of the infusion cannula is directly inserted into the external opening of the microcannula.^{5,6} Once the intraocular position of the infusion cannula is verified, infusion is opened and the other two microcannulas are inserted in the superotemporal and superonasal quadrants for three-port PPV. At the completion of surgery, the microcannulas are simply removed by grasping the collar and withdrawing, along with assessment of intraocular pressure (IOP) and wound sites for possible leaks.

The 23-G system is a variation of the 25-G TSV system. 23-G vitreous cutters have been improved by placing the cutter opening nearer to the end of the probe allowing a closer vitreous shave. This increases safety near the retina. At the end of vitrectomy, adequate gas/air tamponade must be performed which avoids significant postoperative leakage in most cases. However, in some cases leakage may occur and the sclerotomy site should be closed with a single 7-0 or 8-0 vycril suture. In addition, sclerotomy sites are to be closed if silicone oil is used. The microcannulas can be simply removed by grabbing the external collar with a forceps at the end of the procedure. The last microcannula to be removed should be the one with the infusion line (Fig. 2). Postoperative subconjunctival injection of antibiotic and steroid solutions should be administered as in standard vitrectomy. Endophthalmitis is extremely uncommon following vitreous surgery, but there is a theoretical concern that 25-G sutureless surgery may pose an added risk.⁷ However, these concerns have

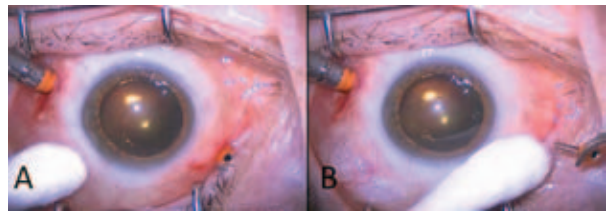


Figure 2. After withdrawal of the cannula, a cotton tip applicator can be used to misalign the outer and inner aspects of the sclerotomy thereby reducing the risk of leakage.

subsided due to recent studies revealing a low incidence of endophthalmitis in a large series of patients undergoing small-gauge sutureless surgery.⁸

Advantages of Small-gauge Vitrectomy

In general, TSV seems to be particularly advantageous for procedures that do not require extensive intraocular tissue dissection or manipulation. Experience has shown that 25-gauge surgery is ideal for vitreous and preretinal hemorrhages in proliferative diabetic retinopathy (Fig. 3), rhegmatogenous retinal detachment, proliferative vitreoretinopathy (PVR), giant retinal breaks, and cases in which vitrectomy and phacoemulsification are combined with intraocular lens (IOL)

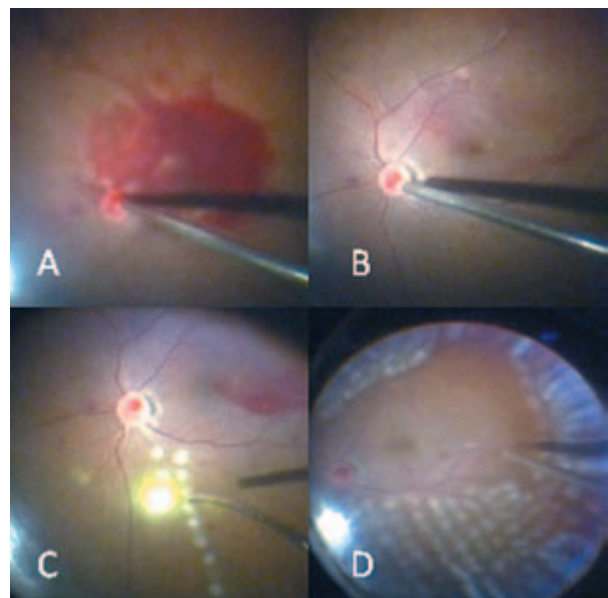


Figure 3. Intraoperative photographs of a diabetic eye with vitreous and preretinal hemorrhages managed with 23-gauge instrumentation.

implantation. It is also applicable for diabetic traction retinal detachment with moderate amounts of epiretinal membranes (ERMs), and idiopathic ERMs as well (Fig. 4). However, if scleral buckling or silicone oil tamponade is anticipated, standard 20-G vitrectomy is preferred as its full capability may be required in those cases. Even in complex cases where one needs a variety of scissors and forceps and/or the injection of silicone oil, 25-G or 23-G sclerotomies can be used for the infusion and illumination probes, and a 20-G sclerotomy can be performed for the instruments and the injection and removal of silicone oil. This enables the surgeon to use 20-G instruments and reduce the cost of replacing all devices.⁹ An alternative is to use 1000 centistoke silicone oil with 23-G instrumentation, therefore even

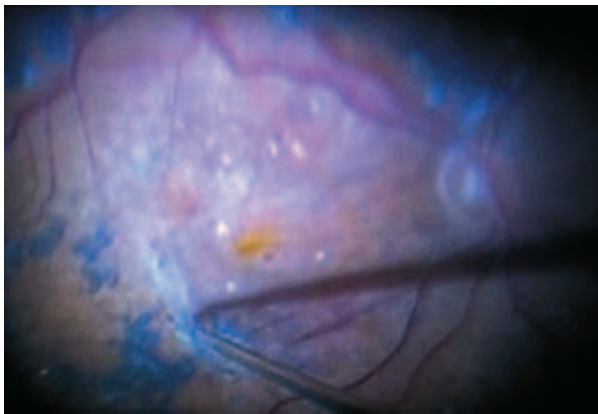


Figure 4. Intraoperative photograph of macular epiretinal membrane treated with 23-gauge instrumentation.

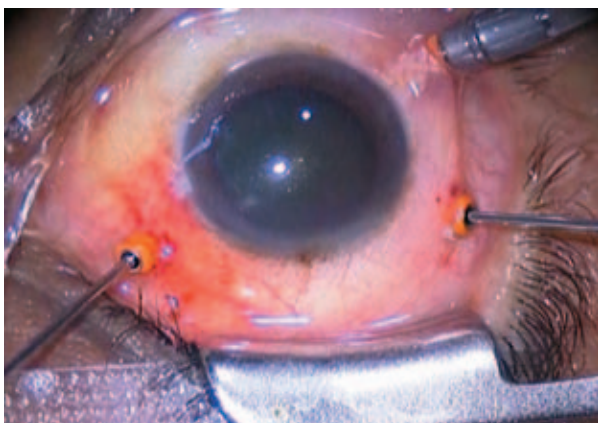


Figure 5. The microcannulas are inserted through the conjunctiva into the eye and 23-gauge instruments are in place at the sclerotomy sites.

complex cases can be resolved with small-gauge surgery.

Another advantage of TSV becomes apparent in pediatric cases. Typically, newborn and premature eyes are significantly smaller than adult eyes and the use of standard vitreoretinal instruments may be technically difficult.¹⁰ With TSV, the intraocular instruments are more compatible with the smaller pediatric eyes and are efficient in selected cases of persistent fetal vasculature, retinopathy of prematurity, uveitis, and some cases of uncomplicated tractional or rhegmatogenous retinal detachments. In addition, TSV offers benefits in certain vitreoretinal cases because it is transconjunctival. TSV-based surgery has the potential to shorten operative time for a variety of procedures, and reduce postoperative inflammation at the sclerotomy sites (Fig. 5), thus reducing patient discomfort and hastening postoperative recovery. It also avoids induced astigmatism, allowing more rapid visual recovery.¹¹

Disadvantages of Small-gauge Vitrectomy

One disadvantage of this system is the learning curve required to achieve maximum efficiency. However, this curve is short enough for the adaptable surgeon.

Due to its smaller fiberoptic size, illumination is also reduced with 25-gauge surgery. However, current systems provide adequate illumination in most cases. A noticeable difference of 25-G instruments is their marked flexibility.

There are some potential complications specifically related to the 25-gauge system, the most obvious being hypotony and a higher incidence of endophthalmitis.⁷ The risk of these complications can be reduced by creating a tunnel or angular incision in a different plane relative to the conjunctiva, and performing fluid-air exchange at the end of the surgery. It is important to note that hypotony is more common in previously vitrectomized eyes. As mentioned, these concerns have been diminished as a result of recent studies demonstrating a low incidence of endophthalmitis in large series of patients undergoing TSV.⁸ In terms of

prophylaxis, all patients undergoing 25-gauge vitrectomy should have standard and meticulous preparation with povidone-iodine, as well as postoperative injection of subconjunctival antibiotics.

For a surgeon used to performing 20-G vitrectomy, transition to 23-G is easier than 25-G. With the 23-G system, rigidity, flow and aspiration of the vitreous cutter are similar to the 20-G system, and lighting is comparable. The instruments have stiffness similar to 20-G. However the sclerotomies must be precisely formed, with tunnel or angular incisions to reduce complications.

Recent Advances in 23- and 25-gauge Surgery: Overcoming the Disadvantages

Instrument Rigidity

The lower rigidity of instruments is a problem with 25-G, these instruments are more pliable and more damageable, furthermore manipulation of the globe can become cumbersome. This is not an issue with 23-G, as rigidity is similar to 20-G (Fig. 5). Several companies are producing more rigid 25-G instruments (including the new Alcon Constellation system; Alcon Laboratories, Fort Worth, TX, USA) or are reducing instrument length to achieve the same purpose.

Instrument Availability

Initially, available instruments were limited to small-gauge forceps, however nowadays a full armamentarium of instruments is available in small-gauge, including extrusion cannulas for silicone oil injection and removal, scissors, dual-bore cannulas for perfluorocarbon injection, diathermy probes, multidirectional laser probes, chandeliers, and 40-G cannulas for subretinal injections. In essence, at present, the same range of instruments used in 20-G, is available in 23- and 25-G, with the exception of a fragmatome. Nevertheless, several companies are working on developing a 23-G fragmatome to address dislocated nuclei, and DORC (Zuidland, The Netherlands) has recently released the 23-gauge Rayes Fragmentation Needle.

Illumination

Since the number of light fibers is reduced, particularly with 25-G, brighter light sources are needed, such as Photon (Synergetics Inc., O'Fallon, MO, USA) and Xenon (Alcon Laboratories, Fort Worth, TX, USA). The new Alcon Constellation system has much brighter light than the actual Xenon. Bausch & Lomb (Rochester, NY, USA) uses the Photon. With these recent modifications, illumination is not much of an issue anymore.

Cutting Efficiency

Slow vitreous removal is a potential problem with 25-G, this issue has been addressed in the new Alcon Constellation machine. The new 25-G probe has a bigger opening and a longer duty cycle (the amount of time the port is open); these alterations allow an increased aspiration rate while maintaining high-speed cutting rates. The 23-G system will benefit from the same duty cycle improvement, but the probe is different and does not have a spring mechanism, so it can stay open longer during each cut, allowing greater aspiration. Thus the rapidity of vitreous removal with 23- and 25-G will be markedly improved. Cutting rates of up to 5000 cuts/min are available, allowing for shaving of the vitreous base and safer vitrectomy, even in detached retinas.

Wound Architecture

Wound architecture is the most important aspect of TSV; complications such as endophthalmitis and retinal breaks are associated with badly fashioned wounds. Initially, wounds for 25-G vitrectomy were made by direct entry, this could have been the cause of hypotony and increased endophthalmitis rates among other complications. Displacement of the conjunctiva and a two-plane wound with fluid-air exchange at the end of the procedure, reduce wound leaks and decrease the risk of endophthalmitis and hypotony. The DORC and new Alcon 23-G TSV systems have a flat blade trocar system which produces a slit wound that closes better than

the actual chevron wound made by the round trocar blade system. Wound construction in our view is the most important aspect of TSV and the key point in the learning curve. One should always keep in mind that if any doubt exists regarding leakage, the surgeon should suture the sclerotomy site. Our threshold for tends to be lower in complicated cases where silicone oil needs to be used.

Surgical Outcomes

Other benefits of TSV include astigmatism-neutral surgery, shortened operative time, less inflammation and reduced patient discomfort. We truly believe that the reportedly increased incidence of endophthalmitis is technique-dependent. With adequate preoperative povidone-iodine preparation, good wound construction in two planes, a partial or total fluid-air exchange at the end of the procedure, and subconjunctival antibiotics, the risk of hypotony and endophthalmitis can be reduced.

Learning Curve

The learning curve is mainly due to wound construction and for 25-G, the current lack of rigidity. The TSV 23-G system has less of a learning curve, as the instruments have similar rigidity as 20-G. The 23-G system has been more user-friendly due to the illumination, rigidity, and increased flow, which are all similar to 20-G. With improvements in 25-G systems, at least with the Constellation system, 25-G surgery will feel more like 23-G, as rigidity, aspiration, and illumination are increased significantly.

Summary

Cataract surgery was revolutionized by the introduction of phacoemulsification and foldable IOLs. This enabled a reduction in the size of the incision and avoided the necessity of using sutures. This transition shortened operative time, reduced complications, and increased patient satisfaction and comfort.

The same transition is occurring in vitreous surgery. Both vitrectomy techniques,

either 25-G or 23-G, have been improving with time, experience, and the introduction of better instruments. Surgical indications are expanding with experience and the availability of new technology. Performing minimally invasive surgery has many advantages for both the surgeon and the patient. The reduced surgical time improves efficiency and also reduces complications and surgical trauma. Postoperative recovery is more rapid, since there is less inflammation. Technological developments, more efficient vitreous cutters, and a variety of 23-G and 25-G instruments have made small-gauge vitrectomy the gold standard and it is here to stay.

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Conflicts of Interest

Dr Arevalo and Dr Arias: None. Dr Berrocal is a speaker for Alcon.

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REFERENCES

1. Machemer R, Buettner H, Norton EW, Parel JM. Vitrectomy: a pars plana approach. *Trans Am Acad Ophthalmol Otolaryngol* 1971;75:813-820.
2. Fujii GY, De Juan E Jr, Humayun MS, Pieramici DJ, Chang TS, Awh C, et al. A new 25-gauge instrument system for transconjunctival sutureless vitrectomy surgery. *Ophthalmology* 2002;109:1807-1812.

3. Fujii GY, De Juan E Jr, Humayun MS, Chang TS, Pieramici DJ, Barnes A, et al. Initial experience using the transconjunctival sutureless vitrectomy system for vitreoretinal surgery. *Ophthalmology* 2002;109:1814-1820.
4. Eckardt C. Transconjunctival sutureless 23-gauge vitrectomy. *Retina* 2005;25:208-211.
5. Inoue M, Shinoda K, Shinoda H, Kawamura R, Suzuki K, Ishida S. Two-step oblique incision during 25-gauge vitrectomy reduces incidence of postoperative hypotony. *Clin Experiment Ophthalmol* 2007;35:693-696.
6. López-Guajardo L, Vleming-Pinilla E, Pareja-Esteban J, Teus-Guezala MA. Ultrasound biomicroscopy study of direct and oblique 25-gauge vitrectomy sclerotomies. *Am J Ophthalmol* 2007;143:881-883.
7. Taylor SR, Aylward GW. Endophthalmitis following 25-gauge vitrectomy. *Eye (Lond)* 2005;19:1228-1229.
8. Scott IU, Flynn HW Jr, Acar N, Dev S, Shaikh S, Mitra RA, et al. Incidence of endophthalmitis after 20-gauge vs 23-gauge vs 25-gauge pars plana vitrectomy. *Graefes Arch Clin Exp Ophthalmol* 2011;249:377-380.
9. Shimada H, Nakashizuka H, Mori R, Mizutani Y. Expanded indications for 25-gauge transconjunctival vitrectomy. *Jpn J Ophthalmol* 2005;49:397-401.
10. Gonzales CR, Boshra J, Schwartz SD. 25-Gauge pars plicata vitrectomy for stage 4 and 5 retinopathy of prematurity. *Retina* 2006;26:S42-S46.
11. Okamoto F, Okamoto C, Sakata N, Hiratsuka K, Yamane N, Hiraoka T, et al. Changes in corneal topography after 25-gauge transconjunctival sutureless vitrectomy versus after 20-gauge standard vitrectomy. *Ophthalmology* 2007;114:2138-2141.

CON

The large leap in surgery during the past few decades has been its progress towards becoming more minimal and less destructive. Laparoscopic surgery is a prototype of this change. This concept has also provided immense changes in ophthalmic surgical techniques: transition from intracapsular to extracapsular cataract surgery with implantation of IOLs, followed by less invasive phacoemulsification with foldable IOLs, and finally, minimally invasive cataract surgery.

But what about vitreoretinal procedures? Have these operations also moved in same

direction of becoming less invasive and more minimal? With no doubt, the answer is yes. The change in buckling techniques from implants to explants, the trend to use segmental buckles instead of encircling elements, and the use of pneumatic retinopexy or vitrectomy instead of scleral buckling are all signs of attempts to do less extensive, but more effective procedures. One of the greatest changes in this field during the last two decades has been the introduction of minimally invasive vitreoretinal surgery (MIVS), which by using 23- or 25-gauge instruments, allows a sutureless procedure.^{1,2}

Although most vitrectomy cases are suitable candidates for sutureless vitrectomy, not all patients can be handled "sutureless". Examples include extraction of a large intraocular foreign body in a case with a clear lens, and eyes requiring scleral buckling in addition to vitrectomy. Clearly, these constitute only a minority of current vitrectomy cases. There are other situations in which the use of sutureless techniques with its small-gauge instruments still poses limitations, such as the absence of a full range of multifunctional instruments in small-gauge for complicated retinal detachments and diabetic retinopathy, flexibility of the instruments when maneuvers in the retinal periphery become necessary, inability to overcome dense thick membranes with small-gauge instruments, and the injection and removal of silicone oil, especially of high viscosity. In most of these situations, the case cannot be managed with self-sealing sclerotomies.

I am aware of the fact that the mentioned limitations are being solved by technological advances and will no longer be a problem in the near future. But let's look at the question from another perspective.

The question whether sutureless vitrectomy is the future of vitreoretinal surgery is similar to asking whether phacoemulsification is the future of cataract surgery. I think almost everyone would agree on a negative answer. Why? Because we already have it and use it regularly. It is not the "future" of cataract surgery, it is the current state. Although phacoemulsification has been a large progress

towards minimization of cataract surgery, everybody knows that phacoemulsification is still not the best minimal surgery and ophthalmologists are looking forward to enzyme-assisted phacolysis along with the injection of liquid IOLs as a realistic goal. The same also applies to sutureless vitrectomy techniques. These techniques present a state of the art procedure, and will certainly be a the predominant method for the next few years, but they are not the “future” of vitreoretinal surgery, just as phacoemulsification is not the future of cataract surgery. In my opinion, the future is in the hands of injections, along with preventive and personalized ophthalmology.

We now know that the vitreous is not only a clear substance for filling a cavity; it plays many physiological roles, the most clearly known is oxygen absorption and prevention of oxidative damage to intraocular structures.³ Eyes undergoing vitrectomy are prone to the development of nuclear sclerotic cataracts and open angle glaucoma, probably due to augmented oxidative damage.⁴ Therefore removal of the vitreous may not always be desirable. If a treatment or preventive measure becomes available that by producing syneresis preserves gel vitreous, it will surely be a better option than surgery for many of current indications for vitrectomy.

A common saying in medicine is “prevention beats treatment”. Surely, progress in medical knowledge and resources will move the medical community more and more towards “preventive medicine”. To achieve prevention, one must first recognize those at risk, and personalized medicine will prove a powerful tool in this regard. In the personalized medical strategy, which is the beginning of a new era in all medical fields, information based on evaluation of genetic variations and expression profiles, proteins, and markers, is used to deliver targeted treatment or enforce prevention. Recognizing patients at risk for developing various diseases and obtaining knowledge on how the disease and the response to treatment is expressed or modified by the genetic background of the patient, are turning this idea into reality.^{5,6} It is conceivable that in the future, we may

be able to recognize genes causing abnormal vitreoretinal adhesions in patients developing vitreoretinal interface problems, macular holes, and retinal breaks after posterior vitreous detachment (PVD). We may even become able to recognize diabetics at risk of developing proliferative disease by evaluating their genetic background, and apply preventive measures in susceptible cases.

Chemical vitreolysis has drawn the attention of vitreoretinal surgeons for many years.⁷ Many agents have been examined in this regard: hyaluronidase⁸, autologous plasmin^{9,10}, tissue plasminogen activator^{11,12}, various enzymes^{13,14}, and more recently, microplasmin¹⁵. But why chemical vitreolysis? Because injection is easier and less time-consuming than an operation, it creates a smoother surface with a lower risk of re-proliferation, and is less traumatic to the retina. Microplasmin is a synthetic recombinant form of truncated plasmin which cleaves fibronectin and laminin molecules at the vitreoretinal interface.¹⁶ In a randomized clinical trial, a single injection of microplasmin in eyes with vitreomacular traction, induced PVD in 44% of eyes 28 days after the injection, and in 58% after multiple injections.¹⁵

With the discovery of additional targeted molecules, chemical vitreolysis will surely open its way as a safe and effective procedure. Targeted treatment to weaken the vitreoretinal junction without causing separation from the retina may become possible in the near future. This may have merit for prophylaxis against retinal break formation by PVD in susceptible eyes. Prevention of retinal break formation would circumvent one of the major indications for vitrectomy, i.e., retinal detachment and PVR. The same goal may prove desirable in those predisposed to macular hole formation and other vitreoretinal interface abnormalities. In other situations, such as diabetic retinopathy, it may be preferred to induce complete PVD in order to prevent new vessel growth into the vitreous cortex before development of proliferative retinopathy. By preventing proliferative diabetic retinopathy and its complications, one of the most common indications for vitrectomy will be avoided.

It seems that personalized medicine, along with advances in the field of chemical vitreolysis, will help ophthalmologists prevent many of the current indications for vitrectomy in the future. I admit that in spite of all the mentioned strategies, the need for vitrectomy surgery will remain for some cases.

Injections can also be used for other purposes, such as gene therapy, stem cell therapy, and the delivery of slow-release drug implants. These strategies may pave the road for treatment or prevention of many currently untreatable diseases, such as retinal degenerations and end-stage glaucoma.

With the preventive measures mentioned, hopefully only a few cases will require buckling surgery. Injectable and degradable materials are eligible candidates for use in scleral buckling. Polymers that are liquid at room temperature, but become solid at body temperature, can be injected into the globe overlying a retinal break with the guide of indirect ophthalmoscopy. These liquids can be made of biodegradable materials to minimize long-term anatomical alterations, such as corneal aberrations.¹⁷

Injections are simple, do not have a learning curve, do not need much anesthesia, are fast and cheap, and can be performed in outpatient settings. They are obviously much more acceptable to patients than surgery. They are much more efficient in terms of time and money, and are much less disturbing to the patient, care providers and the eye. This is why I consider them to be the future of vitreoretinal surgery.

Conflicts of Interest

None.

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REFERENCES

1. Fujii GY, De Juan E Jr, Humayun MS, Pieramici DJ, Chang TS, Awh C, et al. A new 25-gauge instrument system for transconjunctival sutureless vitrectomy surgery. *Ophthalmology* 2002;109:1807-1812.
2. Eckardt C. Transconjunctival sutureless 23-gauge vitrectomy. *Retina* 2005;25:208-211.
3. Holekamp NM. The vitreous gel: more than meets the eye. *Am J Ophthalmol* 2010;149:32-36.
4. Holekamp NM, Shui YB, Beebe DC. Vitrectomy surgery increases oxygen exposure to the lens: a possible mechanism for nuclear cataract formation. *Am J Ophthalmol* 2005;139:302-310.
5. Ackerman MJ. Personalized medicine. *J Med Pract Manage* 2009;25:194-195.
6. Wassélius J, Johansson K, Håkansson K, Abrahamson M, Ehinger B. Cystatin C uptake in the eye. *Graefes Arch Clin Exp Ophthalmol* 2005;243:583-592.
7. Sebag J. Pharmacologic vitreolysis. *Retina* 1998;18:1-3.
8. Zhi-Liang W, Wo-Dong S, Min L, Xiao-Ping B, Jin J. Pharmacologic vitreolysis with plasmin and hyaluronidase in diabetic rats. *Retina* 2009;29:269-274.
9. Rizzo S, Pellegrini G, Benocci F, Belting C, Baicchi U, Vispi M. Autologous plasmin for pharmacologic vitreolysis prepared 1 hour before surgery. *Retina* 2006;26:792-796.
10. Wang ZL, Zhang X, Xu X, Sun XD, Wang F. PVD following plasmin but not hyaluronidase: implications for combination pharmacologic vitreolysis therapy. *Retina* 2005;25:38-43.
11. Murakami T, Takagi H, Ohashi H, Kita M, Nishiwaki H, Miyamoto K, et al. Role of posterior vitreous detachment induced by intravitreal tissue plasminogen activator in macular edema with central retinal vein occlusion. *Retina* 2007;27:1031-1037.
12. Yamamoto S, Sugita S, Sugamoto Y, Shimizu N, Morio T, Mochizuki M. Quantitative PCR for the detection of genomic DNA of Epstein-Barr virus in ocular fluids of patients with uveitis. *Jpn J Ophthalmol* 2008;52:463-467.
13. Takano A, Hirata A, Ogasawara K, Sagara N, Inomata Y, Kawaji T, et al. Posterior vitreous detachment induced by nattokinase (subtilisin NAT): a novel enzyme for pharmacologic vitreolysis. *Invest Ophthalmol Vis Sci* 2006;47:2075-2079.
14. Wang F, Wang Z, Sun X, Wang F, Xu X, Zhang X. Safety and efficacy of dispase and plasmin in

- pharmacologic vitreolysis. *Invest Ophthalmol Vis Sci* 2004;45:3286-3290.
15. Stalmans P, Delaey C, de Smet MD, van Dijkman E, Pakola S. Intravitreal injection of microplasmin for treatment of vitreomacular adhesion: results of a prospective, randomized, sham-controlled phase II trial (the MIVI-IIT trial). *Retina* 2010;30:1122-1127.
16. Hermel M, Dailey W, Hartzler MK. Efficacy of plasmin, microplasmin, and streptokinase-plasmin complex for the in vitro degradation of fibronectin and laminin- implications for vitreoretinal surgery. *Curr Eye Res* 2010;35:419-424.
17. Okamoto F, Yamane N, Okamoto C, Hiraoka T, Oshika T. Changes in higher-order aberrations after scleral buckling surgery for rhegmatogenous retinal detachment. *Ophthalmology* 2008;115:1216-1221.