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Perspective

Virtual Reality Becomes a Reality for Ophthalmologic Surgical Clinical Trials

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The Port Delivery System with ranibizumab (PDS) is an innovative, investigational drug delivery system designed for continuous delivery of ranibizumab into the vitreous to maintain therapeutic drug concentrations for extended durations. The phase 2 Ladder trial (NCT02510794) tested the efficacy of three customized formulations of ranibizumab in patients with neovascular age-related macular degeneration, and the phase 3 Archway trial (NCT03677934) will further assess the safety and efficacy of PDS 100 mg/mL with fixed 24-week refills. The insertion of the PDS implant into the vitreous cavity and subsequent refill-exchange of the drug require procedural skills that are not directly transferable from everyday experience for most eye surgeons today. Preoperative practice for the PDS implant insertion and refill-exchange procedures is therefore critical for achieving optimal surgical outcomes. Virtual reality (VR) as a training tool has long been used by the aeronautic industry and more recently adapted for physician training in medicine and surgery, with encouraging results. Besides the primary use of traditional training tools, physicians participating in Archway have an option to practice in computer-simulated environments provided by VR simulators before performing their first PDS implant insertion and refill-exchange procedures on patients. This Perspective article describes the unique advantages and technologic challenges that practice on VR simulators has to offer, and the experience of Archway physicians with VR technology as a first in any ophthalmic clinical trial.

Introduction

It is never too late to learn something new. And when it comes to adopting a new surgical procedure, how can we ensure that the expertise is best accomplished in a short period of time? In the last two decades, a number of novel vitreoretinal surgical procedures have been introduced, including retinal translocation, retinal chip implantation, retinal pigment epithelium transplantation, and, more recently, subretinal gene therapy. Recent investigational technologies for intraocular drug delivery have also brought novel surgical procedures to the attention of retinal specialists. One such example is the Port Delivery System with ranibizumab (PDS), which is an innovative, investigational drug delivery system designed for continuous delivery of a customized formulation of ranibizumab into the vitreous. The implant is surgically inserted through the pars plana and subsequently refilled in an office-based procedure. The PDS with three customized ranibizumab formulations was assessed in patients with neovascular age-related macular degeneration in the phase 2 Ladder trial (NCT02510794).[1] After positive results from Ladder, the safety and efficacy of PDS 100 mg/mL with fixed 24-week refills is currently being compared with monthly intravitreal ranibizumab 0.5 mg in the phase 3 Archway trial (NCT03677934) in patients with neovascular age-related macular degeneration.[2]

The insertion of the PDS implant requires an outpatient surgical procedure, where, after scleral dissection and laser ablation of the exposed pars plana and subsequent incision, the filled implant is placed in the vitreous cavity, with the implant flange residing

on top of the sclera in the subconjunctival space of the superotemporal quadrant of the eye. The conjunctiva and Tenon's capsule are meticulously closed to fully cover the implant flange, completing the procedure.[1] Although the overall steps are familiar to eye surgeons today, key parts of the procedure are novel or not commonly performed in vitreoretinal surgeries. These steps are critical to mitigating complications, such as vitreous hemorrhage or conjunctival erosion/retraction, which did occur after implant insertion in a subset of PDS-treated patients in Ladder.[1]

Likewise, the novel, office-based refill exchange of the drug in the PDS implant is a distinct procedure. A self-sealing septum in the center of the flange allows the implant to be refilled with a specialized needle that allows for the simultaneous exchange of the implant contents with fresh ranibizumab. Despite similarities to intravitreal injections, which are performed routinely, with nearly six million injections performed in 2016 in the United States alone,[3] the skills to perform a successful refill exchange are not directly transferable from experience with intravitreal injections. A specific angle between the needle and the implant flange is needed while targeting the center of the septum with the needle. Successful entry of the PDS implant septum requires considerably more precision and attention than a standard intravitreal injection because it must precisely align with the implant and septum.

Virtual Reality (VR) in Ophthalmology

The most important aspects of clinical research are safety and efficacy. To this end, special consideration is necessary when designing and carrying out surgical clinical trials, especially when novel techniques are introduced. Procedural standardization and adherence to the instructions for use of an investigational device are key to success. Surgical procedures that inconsistently adhere to specific instructions in a trial can put patients at risk, reduce the potential benefit of the investigational device, and lead to program delays.

Training for a new procedure is therefore essential and can be provided to surgeons through various techniques, including lectures, brochures, instructional videos, cadaver wet labs, live animal surgical labs, and mentorships. The use of traditional tissue-based wet lab training is well established, time tested, and considered the gold standard for medical training while learning new surgery skills. Over the last 15 years, however, a new and powerful training approach based on VR technologies has slowly emerged but recently gained significant momentum.[4] VR simulators are computer-simulated environments that allow users to undertake procedural tasks and experience various associated scenarios in a risk-free environment. They have been used for many decades in the aeronautic industry, and all commercial pilots are initially cleared on VR training programs before flying in reality. VR adoption in health care is a more recent phenomenon and has been implemented in a variety of applications, ranging from physician training to treatment of combat-related post-traumatic stress disorder.[5–9] The advent and rapid improvement of VR platforms has transformed many institutional medical and surgical training programs as they work to embrace the versatility of the technology.[10]

In ophthalmology, VR simulators have become highly sophisticated and compelling, using not only excellent three-dimensional visual recreations of the procedures that rival the best of VR video gaming today, but also haptic feedback that provides the user with procedure-specific realistic resistance.[11,12] The VRmagic Eyesi Surgical simulator (Mannheim, Germany), for example, is a unique VR simulator developed for intraocular surgery training that has been adopted for cataract surgery by most residency training programs in the United States. The introduction of Eyesi simulator training has been associated with reduced rates of complications in trainee-performed procedures, translating to improved outcomes in patients undergoing cataract surgery.[13,14] Similar vitrectomy training simulators are also available, but their use among trainees is currently more limited.

VR as a Training Option in the Archway Trial

The Archway trial of the PDS represents the first use of a VR system as a surgical training option in an ophthalmic clinical trial. Besides the primary use of traditional training techniques, VR technology is being used as an additional tool to assist in training retinal surgeons involved with the PDS implant insertion and refill-exchange procedures. Preoperative practice on the VR system has the potential to enhance surgeons' readiness, preparing them for success with their clinical trial patients by helping them understand the key steps of the techniques before their first operative case. This is especially relevant to multicenter surgical clinical trials with investigators/surgeons recruiting their first or second cases.

The two separate VR simulators developed for the Archway trial of the PDS were designed to use all aspects of the training potential of VR. In cooperation with VRmagic, Genentech, Inc. developed these VR simulator systems as a training option for the PDS implant insertion and refill-exchange procedures. For the implant insertion surgery training simulation, visual feedback is provided via a digital microscope head. For the refill-exchange training simulation, visual feedback is provided via a head-mounted display that allows the surgeon to move freely within a narrow area of the virtual world. Both systems are controlled through customized force feedback devices that emulate the look and feel of the instruments used during the real procedures. A phantom of a patient head is used to provide the necessary hand rest and improve immersion with the virtual scene. The working principle of both systems is illustrated in a video available here (https://www.vrmagic.com/cloud/index.php/s/5xQNC2yZcoy8Sxr). Archway surgeons were given the opportunity to use these simulators before performing their first PDS implant insertion and refill-exchange procedures. Physicians who had previously performed the procedures in Ladder also had the chance to practice PDS procedures on the VR system before participating in Archway and generally felt that the VR simulation was sufficiently realistic for most of the procedural steps and would enhance the learning of the procedures, especially for new investigators.

Why VR Training?

Advantages

There are a number of potential and unique advantages for surgical training with VR. First, the procedure can be broken down into steps. Specific steps can be rehearsed multiple times in quick succession, providing surgeons with an opportunity to develop their skills through repetition.[4,15] Second, the VR scene can be augmented with head-up displays or three-dimensional guidance elements that can potentially assist or direct the surgeon in real time. This provides live, instantaneous feedback that is more intuitive and accurate than any conceivable verbal direction and thus may facilitate learning, especially for complex medical procedures. Additionally, various levels of difficulty and gamification may be introduced to pique interest and encourage usage. There are data to suggest users of VR technology actually learn faster than those learning via standard cadaver exploration and dissection.[10,16]

One advantage unique to VR compared with traditional surgical training techniques is the ability to collect meaningful quantitative data that can be used to assess user performance and predict transfer of skills.[17,18] The availability of such metrics of VR users can allow for creation of better instructional presentation and training parameters, as well as monitoring the learning progress of the user. The data collected can be quite granular and include information about wound construction, tensions applied to tissues, and accuracy of laser applications. These data can then be presented to the physician to facilitate learning and may be included in a test of surgeon competency before proceeding to the next step or live surgery. Retrospectively, these types of data can be used in a surgical clinical trial to determine whether various levels of competency at the time of training were associated with specific outcomes or rates of complications in the clinical trial patients. Initial feedback from investigators in the phase 3 Archway trial suggests positive applications of the VR technology, including realistic intraoperative scenarios, uniformity in teaching key procedural points, a cleaner training environment with ease of repetition of and exposure to important surgical aspects, and a deeper user understanding of the procedure.

Limitations

Although there can be both real and perceived downsides to VR technology, the primary shortcoming of VR training is cost.[10,15] Developing life-like VR simulations is expensive. Furthermore, the running costs of the simulators themselves are also high, limiting the number of available simulators. Another limitation can be that of having the physical space to house, set up, and use the VR system itself. Ideally, each investigator would have easy, unlimited access to the simulators, but the cost and portability of the simulators limit this. Future technologic advances should help with both of these issues. To address these shortcomings in Archway, VR simulators were made available at investigator meetings and major retinal conferences, providing all investigators with an opportunity to use them. Additionally, although the technology has significantly improved over the last decade, some still feel it falls short of giving the same tissue sensitivity and tactile feedback of traditional wet lab trainings with donor or other procured tissues.[15] In Archway, we observed that some users did not prefer to practice on the VR simulators, stating that the sensation and sensitivity of the haptic instruments were not realistic; however, for some, this became less of an issue after more experience using the system. It has also been noted that

some people are not physically comfortable in the VR environment.[16]

Conclusion

Should the PDS become commercially available, the training of a large number of retina specialists will be necessary. To maximize the safety and efficacy of the device, procedural consistency and adherence to the specified surgical methodology must be maintained in the generalized retinal community, which may be accomplished through scalable VR training. With the growing use of VR in surgical trials and an increasing number of companies embracing it in the training of their investigators, universal adoption of VR as a training option for residents and fellows seems imminent, with retina specialists likely to be spending more of their waking hours in simulated worlds.

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