OPEN

FIRST-IN-HUMAN CLINICAL STUDY TO INVESTIGATE THE EFFECTIVENESS AND SAFETY OF PARS PLANA VITRECTOMY SURGERY USING A NEW HYPERSONIC TECHNOLOGY

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Purpose: Investigate the effective performance and safety of a new hypersonic vitrector technology.

Methods: Postapproval, prospective, single-arm, noncomparative, open-label study at one clinical site in India. Indications: macular hole (9/20), vitreous hemorrhage (7/20), vitreomacular traction (3/20), and vitreomacular traction with pseudomacular hole (1/20). Safety endpoints included intraoperative and postoperative adverse events. Effective performance endpoints were surgeon-rated effectiveness, range of surgical time, and device settings. Other performance measures were preoperative and postoperative best-corrected visual acuity, slit-lamp and indirect ophthalmoscopy, applanation tonometry, color fundus photography, fundus fluorescein angiography, and spectral domain optical coherence tomography.

Results: Core vitreous removal (20/20 subjects), peripheral vitreous removal (18/20), and posterior vitreous detachment induction (13/15) surgeries were successfully completed. Total surgical time was 22.5 minutes to 106 minutes. Serious adverse events through 3 months were 2 device-associated retinal tears and detachment (one intraoperative) and one unrelated postoperative enlargement of macular hole with subretinal fluid.

Conclusion: This first-in-human study suggests that this new hypersonic vitrector technology is a promising alternative to commercially available guillotine vitrectors. The hypersonic vitrector was effective in core vitreous removal in all cases. Larger-scale studies are required to expand on our initial findings for induction of a posterior vitreous detachment or peripheral vitrectomy.

RETINA 40:16–23, 2020

Current standard-of-care vitrectomy technology for the removal of vitreous is based on guillotine vitrector handpieces that aspirate vitreous into an open port, cuts vitreous fibers that have passed through the port, and then removes them through further aspiration. Guillotine vitrector handpieces are generally considered to be safe and effective. Although technological advances have enabled the production of smaller-gauge guillotine vitrector handpieces with faster cut rates, these vitrectors invariably induce traction on the vitreous humor and tractional forces generated through the movement of vitreous fibers into a guillotine vitrector port before their sectioning also poses an inherent risk to the retina as the cutting device approaches it. It has been noted the likelihood of retinal traction resulting in a tear or displacement increases as the operational distance of the guillotine vitrector from the retina decreases.[1]

New developments in hypersonic technology have led to a unique hypersonic vitrector (HV) handpiece (Bausch & Lomb Inc, St. Louis, MO). This technology uses a single lumen needle and therefore allows for the fabrication of smaller-gauge vitrectors with the fluidics of larger-gauge ones.[2] The HV tip has a needle that vibrates at a high ultrasonic frequency sufficient to liquefy the vitreous in front of the port, vitreous then

being aspirated through a permanently open port. The HV handpiece is operated at up to 90% lower amplitude and less than 0.1% of the acoustic energy used by the original ultrasonic vitrector device tested by Girard et al and current posterior fragmentation devices.[3,4] The value of the design and low energy requirements of the HV have been tested on cadaveric porcine and human eyes as well as in live porcine studies[2,5,6] that suggest the HV may be used close to the retina.

The first observations of safety and effective performance of HV probes in conducting human vitrectomies are presented in this report from a clinical study in India. The value of the HV handpiece for clinical use in vitrectomies was shown for patients with prior diagnoses of macular holes, vitreous hemorrhage, or need for a posterior vitreous detachment (PVD). Patients requiring a vitrectomy were enrolled to allow for assessment of the breadth of effective performance for the HV handpiece, including in the near vicinity of the retina. Enrolled patients were followed clinically for 3 months after vitrectomy surgery to determine whether prolonged as well as immediate benefit would be seen with these patients.

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Materials and Methods

This was a single-arm, noncomparative, prospective, open-label, monocular study to assess the safety and performance of a new HV handpiece. The study included 20 eyes of 20 patients requiring vitrectomy. Three retinal surgeons conducted the surgeries on the 20 enrolled patients, with all postoperative visit procedures conducted by one surgeon (A.V.). Nine patients presented with idiopathic macular hole, seven patients with diabetic vitreous hemorrhage, three patients with vitreomacular traction, and one patient with vitreomacular traction involving a lamellar macular hole. All patients were recruited from Agarwal Eye Hospital, Chennai, India, and written informed consent was obtained from all patients before any clinical procedures were performed. Before initiation of the study, the sponsor received documentation of the IRB/EC approval of the protocol and any amendments. The study was conducted in accordance with ISO standard 14155 (2011) for clinical investigations of medical devices. The sponsor also received acceptance of the protocol by the Director Controller General of India (DCGI).

Patients included in the study had to be 40 years of age or older on the date the informed consent form was signed and needed a clinical indication for vitrectomy surgery. Patients also had to have best-corrected visual acuity (BCVA) worse than 20/40 at Visit 1 and be able to undergo imaging studies (optical coherence tomography [OCT], fundus photography, and fluorescein angiography [FA]).

Exclusion criteria for the study removed patients who had participated in any drug or device clinical investigation within 30 days before entry into this study included those patients who had retinal disorders that might confound interpretation of fundus FA or OCT study results, had visual acuity of no light perception at Visit 1, or had uncontrolled glaucoma or ocular hypertension (IOP > 24 mmHg) in the operative eye. Female patients of child-bearing potential who had a positive urine test for pregnancy at Visit 1 also were excluded.

Enrolled patients who met eligibility criteria attended six study visits (including the day of surgery): preoperative visit (1–14 days before the surgery), day of surgery visit, and postsurgical visits at Visit 1 (Day 1), Visit 2 (Day 7/Week 1 ± 2 Days), Visit 3 (Day 30/Month 1 ± 7 Days), and Visit 4 (Day 90/Month 3 ± 14 Days). Month 1 data were considered the primary study outcomes and Month 3 data were considered supportive information.

All patients underwent comprehensive ophthalmologic examinations before and after surgery, including measurement of BCVA, intraocular pressure by Goldmann applanation tonometry, and slit-lamp biomicroscopy of both anterior and posterior segments. Color fundus photography and fundus FA were performed using a TRC-50DX camera (Topcon, Tokyo, Japan), and spectral domain OCT was performed with a Cirrus HD-OCT instrument (Model 5000; Carl Zeiss Meditec, Jena, Germany).

Safety evaluations included results of ophthalmologic examinations and incidences of intraoperative adverse events, postoperative adverse events through postoperative Month 1, and changes in BCVA, including monocular loss of >2 lines BCVA (without pinhole) in the study eye at each of postoperative Week 1 to Month 3 compared with preoperative BCVA.

Clinical performance parameters for the HV were analyzed descriptively: 1) length of time and device settings—stroke length, aspiration, vacuum, and infusion pressure; 2) surgeon-assessed device adequacy for: removal of core vitreous, induction of PVD, removal of peripheral vitreous, and/or removal of vitreous hemorrhage; and 3) percentage of vitreous removed during core vitrectomies that could not be completed with the HV handpiece alone and which required the additional use of a guillotine vitrector handpiece.

All patients underwent 3-port 23 G pars plana vitrectomy with an HV handpiece having one of 3 different port configurations of the HV handpiece: 255 μm ("teardrop"), 225 μm (round), and 175 μm (round) (Figure 1). Surgical steps were identical to those for a 3-port conventional guillotine cutter vitrectomy. Immediately after each operation, surgeons answered a written questionnaire to subjectively assess their perceived effectiveness of the HV relative to their historical experience using a guillotine vitrector. Each surgery was rated using the following scale: 1 = substantially better; 2 = somewhat better; 3 = similar; 4 = somewhat worse; and 5 = substantially worse.

Results

Twenty eyes of 20 patients underwent vitrectomy with the HV. Nine patients had a presurgical diagnosis of idiopathic macular hole, seven patients exhibited a diabetic vitreous hemorrhage, three patients had vitreomacular traction, and one patient had vitreomacular traction with a lamellar macular hole. There were 13 male and 7 female patients, and the mean age of patients was 63.4 (SD ± 8.9) years, with an age range
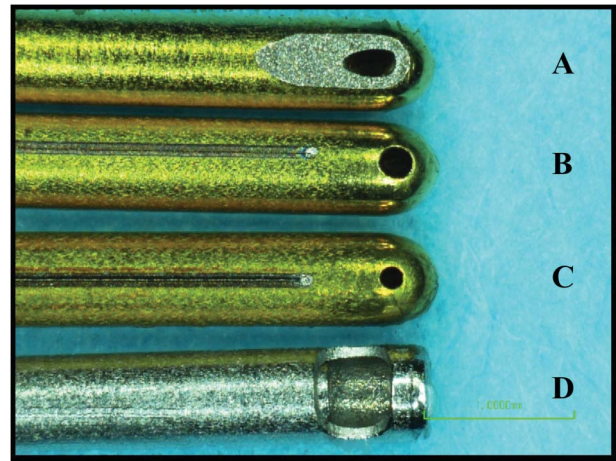

Fig. 1. Representative images of the 23-gauge HV hypersonic vitrectomy probes: (A) HV 255-μm teardrop port; (B) HV 225-μm round port; (C) HV 175-μm round port; and (D) commercially available 23-gauge guillotine (pneumatic) vitrector probe (Bausch & Lomb Inc, St. Louis, MO).

of 40 years to 82 years. All enrolled patients were of Indian origin. Reported antecedent medical history included diabetes mellitus (11/20 patients, 55%), systemic hypertension (10/20, 50%), ischemic heart disease (4/20, 20%), renal disease (3/20, 15%) and hypothyroidism (1/20, 5%).

Total operating time for the surgeries ranged from 22.5 minutes to 106 minutes. Total HV usage time ranged from 3 minutes up to 21 minutes, with an average of about 10 minutes. Settings for the HV ranged among the 20 surgeries as follows: needle stroke ranged from 5.6 μm to 50.7 μm. All surgeries were started with the same needle stroke length and aspiration rate. Average vacuum ranged from 61.8 mmHg to 345.5 mmHg, and up to 600 mmHg of vacuum was used in certain situations. Infusion pressure ranged from 30 mmHg to 33 mmHg.

Core vitreous removal was successfully achieved in all patients with the HV. Induction of a PVD was attempted and achieved in 13/15 (87%) patients. Posterior vitreous detachment induction was not attempted in five patients who had a preexisting PVD. Induction of a PVD was unsuccessful for 2/15 patients (13%), one with preoperative macular pseudohole and one with a macular hole, due to inadequate vitreous purchase by the HV handpiece and strong vitreoretinal adherence.

Peripheral vitreous shaving was attempted and successfully performed in 18/20 patients (90%). In one patient (with a vitreous hemorrhage), the peripheral vitrectomy was not completed due to difficulty in removing dense, organized vitreous hemorrhage near the peripheral retina. In the second patient (with
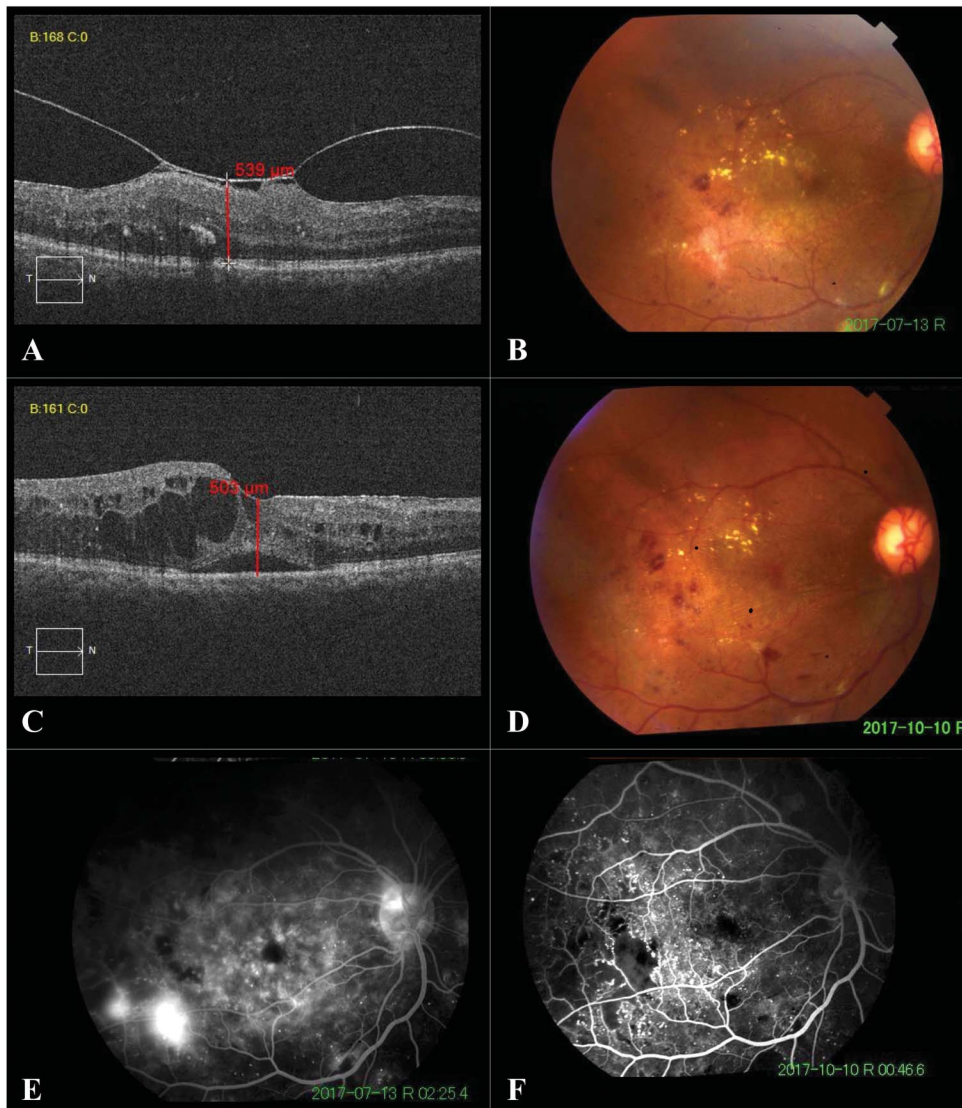
Fig. 2. Proliferative diabetic retinopathy with diabetic macular edema and vitreomacular traction: (**A**) preoperative OCT scans showing vitreomacular traction with a broad foveal attachment; (**B**) corresponding preoperative fundus image; (**C** and **D**) OCT and color fundus photograph at the 3-month postoperative visit after HV peel of internal limiting membrane; (**E** and **F**) preoperative and 3-month postoperative FA ruling out any side effects directly attributable to HV.

a macular hole at screening), intraoperative retinal tear and detachment occurred during a peripheral vitrectomy with the HV and the investigator converted to a guillotine vitrector.

Nine patients underwent vitrectomy for full-thickness macular hole and one patient with a pseudomacular hole. After HV surgery, 9/10 (90%) of the macular holes were shown by multiple diagnostic procedures to be closed at Week 1, whereas 7/10 patients (70%) had their macular holes remain closed at Month 1 and Month 3. Seven patients underwent vitrectomy for vitreous hemorrhage. Six of these patients had clear posterior media at Week 1 and five patients maintained a clear vitreous cavity to Month 1. By Month 3, all patients with preoperative vitreous hemorrhages had vitreous clear of blood; one patient with a preoperative vitreous hemorrhage had only an

organized old subretinal hemorrhage that was resolving at Month 3.

Eight patients presented baseline (preoperative) BCVA worse than 20/200 (Snellen) and only one patient had BCVA of 20/80 or better preoperatively. For the other 12 patients, the mean baseline BCVA was 0.82 (SD ± 0.14) logarithm of the minimum angle of resolution units, corresponding to a Snellen BCVA of 20/132. The mean BCVA at postsurgery Month 1 for 16 patients who could read some of the Early Treatment Diabetic Retinopathy Study chart was 0.60 (SD ± 0.23) logarithm of the minimum angle of resolution units, with 15/16 patients showing improved BCVA and 9/16 patients demonstrating a BCVA of 20/80 or better at Month 1 compared to only 1/20 patients (5%) with BCVA of 20/80 or better preoperatively. By Month 3, all 20 patients could read Early Treatment Diabetic Retinopathy Study chart letters, and

Fig. 3. Full-thickness macular hole: (**A**) preoperative OCT showing Stage 4 macular hole; (**B**) preoperative fundus image; (**C** and **D**) OCT shows complete closure of hole at the 3-month postoperative visit after HV peel of internal limiting membrane and 20% SF6 gas injection.
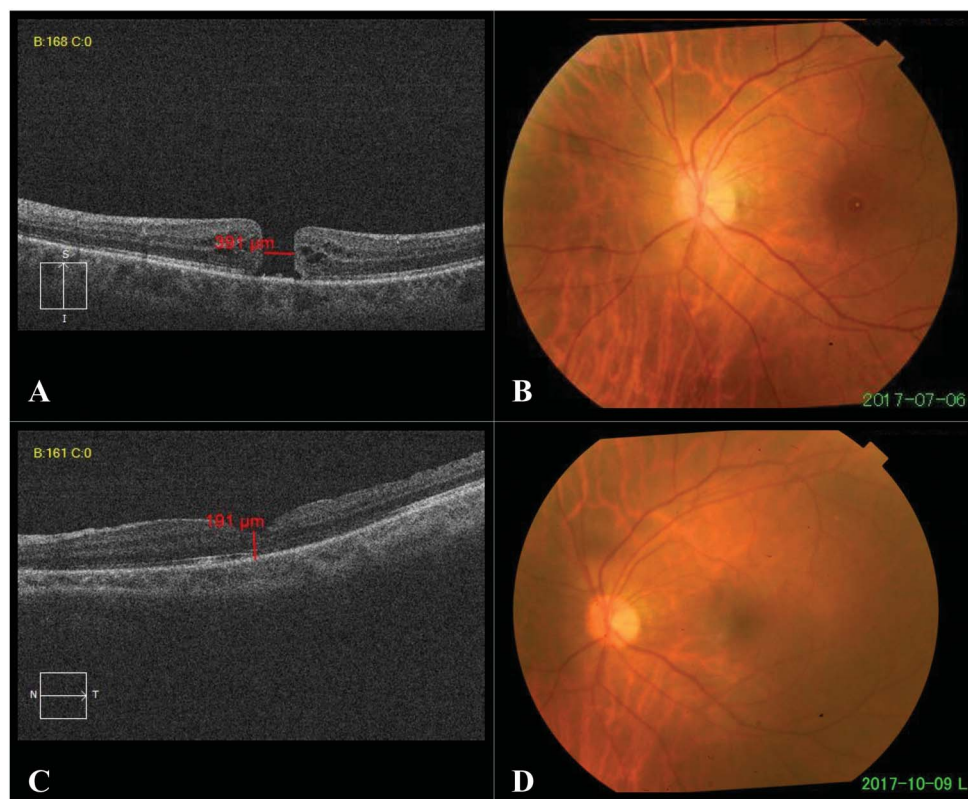
no patient had a vision loss >2 lines of BCVA from their preoperative visit. Mean IOP varied little during the postsurgical period. Mean IOP for the 20 enrolled patients was 14.3 (SD ± 2.8) mmHg on the date of surgery, 15.1 (SD ± 2.6) mmHg at postsurgical Month 1, and 15.5 (SD ± 2.2) mmHg at Month 3. No patient had an IOP value at any study visit greater than 22 mmHg.

The posterior segment for all patients was imaged using OCT, fundus photography, and FA at each study visit, with the objective of monitoring response of the underlying disease process to surgical treatment and to detect any potential side effects of hypersonic energy on the retina or adjacent tissue outside of what would be expected with the use of a guillotine cutter. The OCT findings generally confirmed investigator assessments of the reasons for vitrectomy surgery. The majority of baseline OCT observations showed a full-thickness macular hole or obscured OCT imaging that was judged to be due to a vitreous hemorrhage apparent in fundus photographs. There were 10/20 subjects (50%) that were noted by the investigator over the 3-month study period to have at least one postsurgical pathological change by OCT for at least one study visit in the internal limiting membrane layer, the inner nerve fiber or ganglion cell layers, or in the outer retinal layers. By Month 3, no subject had a pathological change in the internal limiting mem-

brane, five subjects had a change in the inner nerve fiber or ganglion cell layers considered not related to the HV, and one subject had a change recorded for the outer retinal layer (also not related). The OCT findings were in general agreement with indirect ophthalmoscopy and fundus photography findings (Figures 2–4).

Fluorescein angiography was optional at the screening visit and was conducted only for one subject. Fluorescein angiography imaging at Month 1 and Month 3 provided supplementary information on treatment of the underlying retinal disease. As expected, imaging of vitreous hemorrhages was not suitable to be conducted by FA. The medical condition of six subjects also did not allow for FA imaging at Visit 3 or Visit 4, either because of poor medical condition or poor imaging status.

There were six nonserious adverse events and five serious adverse events (SAEs), which affected a total of eight patients observed through Visit 4 (3 months after surgery). Two patients each experienced a retinal tear and a retinal detachment (one intraoperative and one at 1 week after surgery) representing four SAEs that were considered device-associated; the fifth SAE was not considered device-related and was an unclosed macular hole observed at 1 week after surgery that accumulated subretinal fluid around it. None of the SAEs led to patient discontinuation and none of the nonserious adverse events (nonclosure
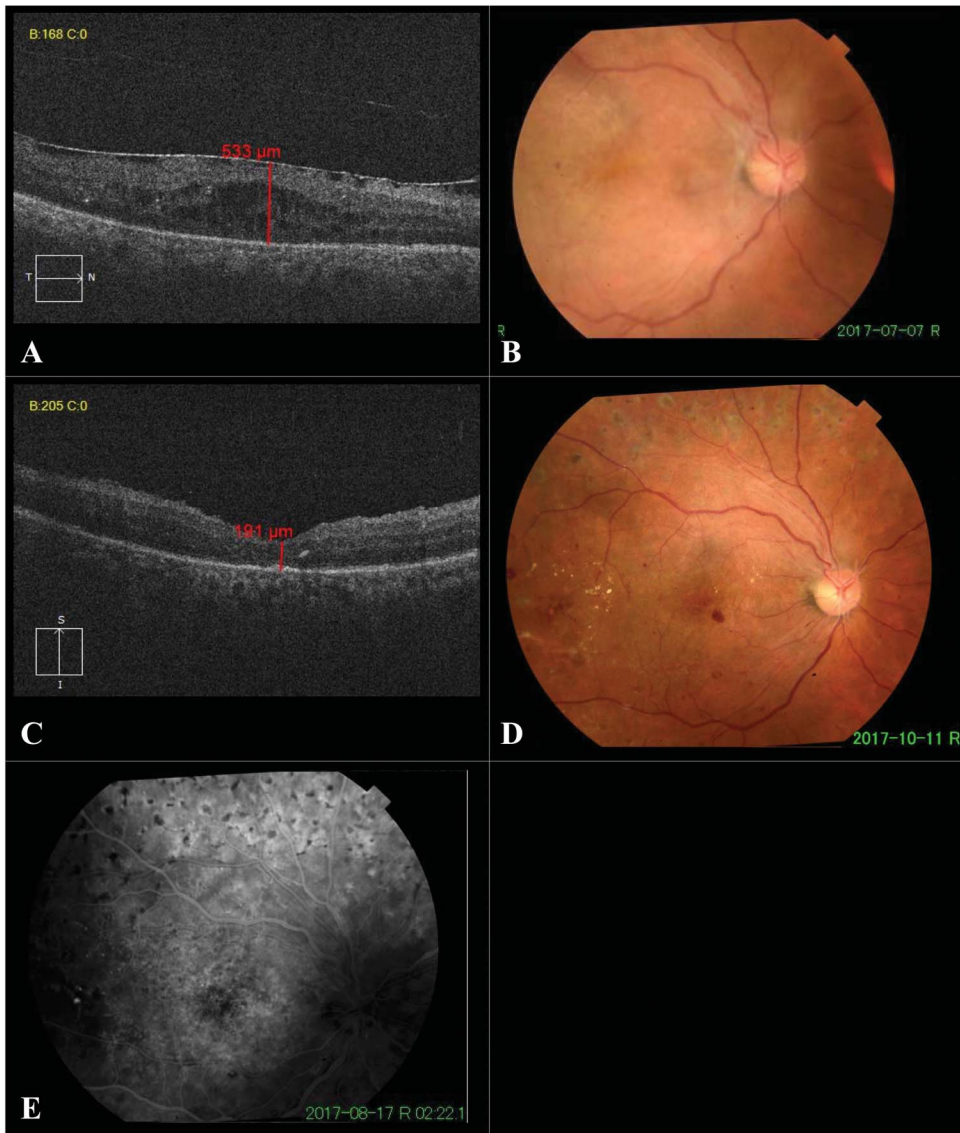
Fig. 4. Nonproliferative diabetic retinopathy with diabetic macular edema and epiretinal membrane: (**A**) Preoperative OCT showing detached posterior hyaloid and epiretinal membrane with diabetic macular edema; (**B**) preoperative fundus image; (**C** and **D**) the 3-month postoperative visit OCT after HV peel of epiretinal membrane showing resolution of the diabetic macular edema and restoration of normal foveal contour; (**E**) postoperative FA.

or enlargement of macular hole, and vitreous hemorrhage) was considered related to the HV.

Mean subjective surgeon rating for the HV immediately after each surgery showed 17/20 (85%) of the HV experiences were rated similar as or better than prior guillotine vitrector experience.

Discussion

Although the birth of systems for vitrectomy surgery dates back to the 1970s,[7] increased cutting rates per minute with improved duty cycle and cutter tip gauge reduction have been arguably the most significant achievements by vitrector manufacturers over the past two decades. Guillotine vitrectors are widely used, although they present a number of limitations, including the port's closure time, retinal traction, mechanical speed limit of the vitrector blade, and turbulence created by the opening and closure of the port.[8–11] Recently, a new generation of spring-return guillotine vitrectors with improved flow characteristics has become available. These more powerful new vitrectors benefit from higher flow rates and increased cutting speeds compared with previously available ones. This potentially reduces the possibility of tractional damage on the retina.[4,12–14]

Ultrasonic vitrectomy was originally conceptualized 40 years ago as a new method to achieve shorter vitreous removal times. The invention and advent of the HV has realized this concept while achieving better port-controlled stability, lower energy, and potentially

allowing for closer approach to the retina due to the more distal placement of the HV port to the tip of the needle.[12] By comparison, it is known that the much greater ultrasound energy from a conventional phacofragmentor can produce morphologic changes in the neuroretina and retinal pigment epithelium when the probe is used in close proximity to them, such as during the removal of a dislocated lens. Such fragmentation performed close to the retina can cause tears in it.[15,16]

This study is the first human study of an HV, a device that uses much less sonic energy than phacofragmentors and recently received clearance from the US Food and Drug Administration. The performance of the HV for performing posterior vitrectomies in this study demonstrated its effectiveness for treating a variety of vitreoretinal conditions. When performing vitrectomy for macular hole repair using the HV, surgeons found that HV was as good or even better than the guillotine headpiece and capable of inducing PVD. Surgeons also observed that staining dyes could be easily injected through the vitrector needle, without the need to exchange instruments. In HV surgeries for vitreous hemorrhage, surgeons were satisfied by effective removal of blood-filled core and peripheral vitreous with limited vitreous traction on the retina.

The majority of vitrectomies in this study (16/20, 80%) used the largest port size HV (255 μm) for the entire procedure. The 225-μm port size HV handpieces were used for the entirety of two surgeries and for part of one surgery. The 225 port was judged adequate except for one case that required a switch to the 255 to complete a peripheral vitrectomy. The 175-μm port size HV was used to initiate two surgeries, but the surgeons found the port too small for effective vitreous removal and switched to the 255-μm port size HV. The surgeons preferred the 255 port for all aspects of surgery and reported that the teardrop configuration allowed for more flow at the same vacuum setting, which provided slightly better aspiration efficiency and vitreous purchase.

Surgeons found some limits associated with the HV. The primary safety concern relates to two subjects who developed retinal tears and detachments. The first case occurred intraoperatively in a subject with screening diagnosis of macular hole. The surgeon reported successful core vitrectomy and PVD induction, but noted that the 175-μm port size HV initially used did not deliver an adequate balance between vitreous liquefaction and aspiration. The surgeon also avoided close proximity to the retina due to the high stroke length (hypersonic power) setting on the device. Due to this feedback, the 175 port was not used in the remaining cases of the study. The second case was observed at 1 week postoperatively, in a subject with screening diagnosis of vitreous hemorrhage. The 255 port was used for the entire procedure and the surgeon reported successful core vitrectomy, PVD induction, and peripheral vitrectomy.

Other issues noted included the length of the current HV handpiece, which may not be capable of reaching the optic disk in eyes with high axial myopia. In addition, vitreous liquefaction was sometimes slow or intermittent, resulting in clogging of the port by vitreous fibers. Vitreous strands extending from the retina to the HV port were observed in a majority of cases. These phenomena became less common when the aspiration rate was lowered, thus allowing more time for the hypersonic energy to liquefy the incarcerated vitreous.

We have defined a complete core vitrectomy as the removal of as much of the central vitreous and peripheral vitreous before induction of PVD. Posterior vitreous detachment was attempted in most enrolled patients and could be accomplished in 13/15 (87%) patients. Due to the first-in-human nature of this study, investigators were cautious and operated HV at low settings which, in combination with strong vitreoretinal adherence common to subjects with a macular hole or an epiretinal membrane, could account for the failure to complete all attempted PVD inductions.

Other limitations of this study were small sample size for judging effective and safe device performance, exclusion of other vitreoretinal conditions requiring vitrectomy (e.g., rhegmatogenous retinal detachment or retained lens fragments), lack of a control group, and variability across surgeries in port configuration and vacuum settings.

The effective performance of the HV has been demonstrated in this clinical study. Larger clinical studies certainly will be needed to determine optimal operational requirements for the HV. Such future studies, preferably multicenter clinical studies, are required to confirm and expand the findings of this pilot study, improve system settings for use of the HV, and expand indications for this new technology.

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