Vitreous Biopsy Under Air: Technique, Complications, and Volume Outcomes

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BACKGROUND AND OBJECTIVE: Classic vitreous biopsy, which targets the vitreous with an undiluted sample of 1 mL to 2 mL, has been used as a diagnostic analysis. Vitrectomy under air infusions have been reported to be able to extract more vitreous sample. In this study, the authors introduce a way of obtaining vitreous sample under air irrigation using 23-gauge vitrectomy and discuss the benefits and potential risks of this procedure.

PATIENTS AND METHODS: In this retrospective case series study, a total of 65 eyes of 65 patients with macular epiretinal membrane (ERM) or macular hole (MH) were enrolled. A vitreous biopsy was carried out with air infusion. Vitrectomy with fluid infusion was then carried out to remove the residual vitreous. Medical records of patients with macular ERM or MH were reviewed and analyzed. Clinical data, including age, sex, best-corrected visual acuity (BCVA), optical coherence tomography (OCT), axial length, presence of posterior vitreous detachment (PVD), presence of liquefication of vitreous, and refraction, were recorded and investigated. The volume of vitreous sample, visual outcome, and complications related to vitreous biopsy at 1-month follow-up were recorded and analyzed.

RESULTS: The mean of undiluted vitreous sample volume was 2.1 mL ± 0.2 mL. There were seven patients whose vitreous samples were less than 2 mL during the vitreous biopsy. The mean age of patients was 62.9 years ± 8.4 years (range: 35 years to 85 years) at diagnosis. There were 18 male and 47 female patients. At 1-month follow-up, no patient had decreased visual acuity. There was one patient who had a peripheral retinal break and was treated with photocoagulation during the operation (1.5%). The insufficient vitreous sample that may occur during the vitreous biopsy under air infusion was related to liquefication of vitreous (28.8%).

CONCLUSION: In summary, vitreous biopsy with air infusion is a safe and effective maneuver to harvest undiluted vitreous in patients without significant vitreous inflammation.

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INTRODUCTION

Vitreous biopsy as a method of diagnostic analysis has been used since the 1970s in the clinical setting for vitreous inflammation and suspected intraocular lymphoma.[1] There are essentially two vitreous sampling methods by pars plana vitrectomy (PPV); one targets the undiluted vitreous with a sample of 1 mL to 2 mL without infusion turned on and the other targets both the undiluted vitreous without infusion turned on and the partially diluted vitreous mixed with infusion fluid in the vitrectomy cassette with infusion turned on.[2] There has also been a report on using 25-gauge transvitreal fine-needle aspiration biopsy for uveal melanoma.[3] It has been reported that PPV specimens mixed with infusion fluid-containing samples from both the center and peripheral vitreous body reveal greater cellularity than undiluted vitreous samples from the core vitreous.[1,4,5] It has also been reported that in case of high viscosity vitreous in proliferative vitreoretinopathy, proteins and peptides collected from a vitreous cutter instrument were superior to that collected from a vitreous needle biopsy.[6]

Vitrectomy and vitreous biopsy under air infusion have been reported using 20- and 25-gauge vitrectomy cutters. It can extract more vitreous sample and can harvest a vitreous sample from the peripheral of the vitreous cavity with a better view of peripheral retinal under air-vitreous face.[7-9] Herein, we introduce a way of obtaining vitreous sample under air irrigation using 23-gauge vitrectomy and discuss the

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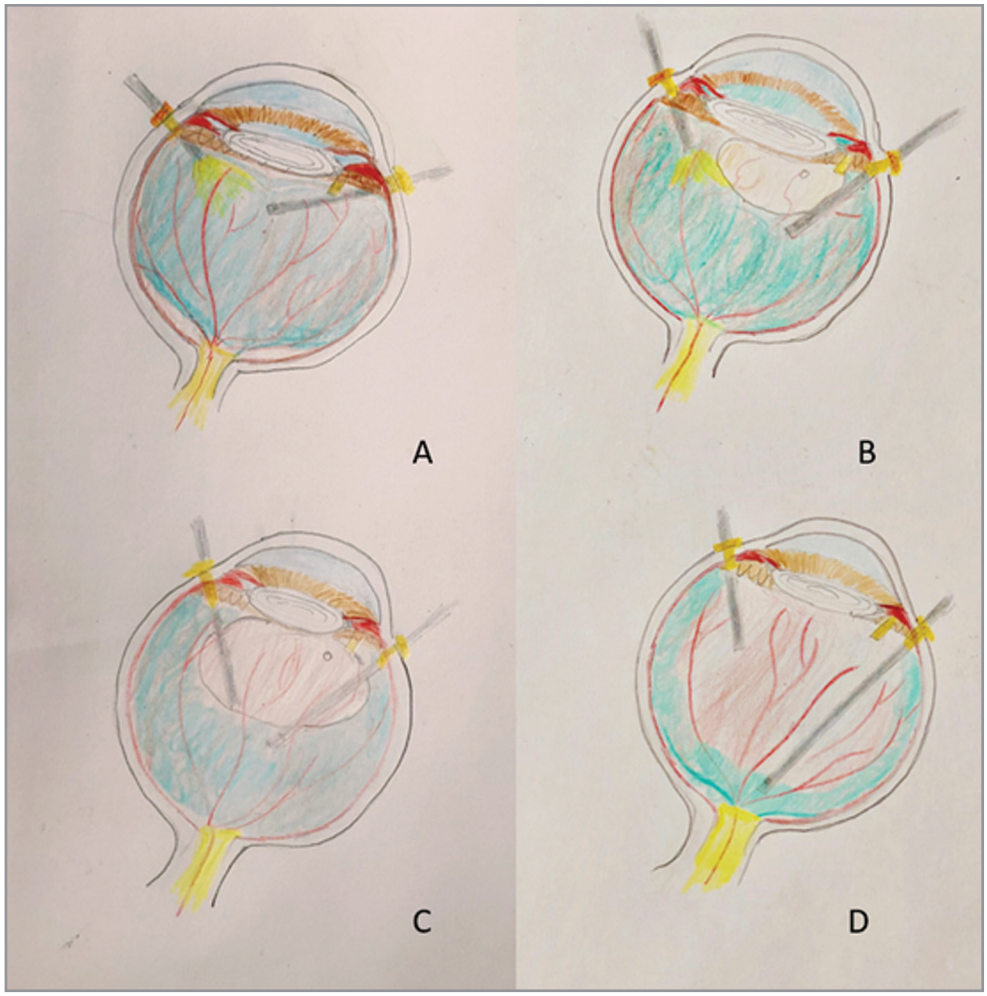

Figure 1. Illustration of vitrectomy biopsy under air in the presence of posterior vitreous detachment (PVD). (A) The biopsy starts with cutting the anterior vitreous body where the PVD is present. (B) The cutter should start to harvest vitreous just behind the air bubble. The air bubble helps to push the vitreous body backward. (C) The cutter cuts the core vitreous body behind the air bubble. In most situations, cutting the middle vitreous body and the inner surface of posterior and peripheral vitreous cortex can meet the need of harvesting 2 mL to 3mL of undiluted vitreous sample. It can help to make the peripheral vitreous cortex and posterior vitreous cortex stable and lessen the traction of vitreous body to the peripheral retina. (D) The peripheral vitreous cortex and posterior virtreous cortex should be left to cut when fluid infusion is turned on.

benefits and potential risks of this procedure, factors that may limit the volume of vitreous sampling.

PATIENTS AND METHODS

This study aims to evaluate the efficacy and safety of vitreous biopsy under air infusion in patients undergoing 23-gauge PPV.

Enrollment of Study Subjects

Records of 146 patients with a diagnosis of macular hole (MH) or epiretinal macular membrane (ERM) who underwent PPV from July 1, 2016, to December 30, 2016, were retrospectively reviewed. The records of 67 patients who were treated by PPV with air infusion turned on first and followed-up for at least 1 month were included. This study was part of research focusing on the proteomic analysis of vitreous from patients with MH and ERM. The result of the proteomic analysis was prepared in another manuscript. This study was approved by the ethics committee of Beijing Tongren Hospital and adhered to the tenets of the Declaration of Helsinki. Inclusion criteria included patients with a diagnosis of MH, vitreous macular traction syndrome, or macular ERM, as well as patients who were currently undergoing PPV. Exclusion criteria included patients who failed to finish at least 1 month of follow-up; patients with refractive error greater than 6.0 diopters (D); patients who underwent ocular surgery, including cataract, trabeculectomy, and scleral buckling, within the last 6 months; patients with secondary macular ERM caused by retinal vasculitis, retinal vein occlusion treated with retinal photocoaculation, proliferative diabetic retinopathy treated with pan retinal photocoagulation, or retinal tear or hole treated by photocoagulation; patients who had traumatic MH; and patients who refused to undergo the vitreous biopsy before PPV.

Examinations at Baseline

All patients underwent comprehensive ophthalmological examinations, including best-corrected visual acuity (BCVA) testing using a decimal visual acuity (VA) chart, slit-lamp biomicroscopy, dilated fundus examination with indirect ophthalmoscopy,

TABLE 1

The Basic Characteristics of Patients Who Underwent Vitreous Biopsy With Air Infusion

Characteristics		Correlation With Vitreous Sample Volume (*P* Value)
Age of diagnosis (years) mean ± SD	62.9±8.4(35-85)	.43
Sex (male, n, %)	18, 27.7%	.76
Diagnosis (n, %)	37, 56.9%	.98
Epiretinal memerbrane	20, 30.8%	
Macular hole	45, 69.2%	
Stage 1	5, 7.7%	
Stage 2	3, 4.6%	
Stage 3	37, 56.9%	
Operation (n, %)	.75	
PPV	14, 21.5%	
Phacoemulsification combined with PPV	51, 78.5%	
BCVA (median, first quality, third quality)	0.1, 0.05, 0.2	.17
Eye lateral (right, n, %)	31, 47.7%	-
Axial length (mm) mean±SD	23.35 ± 1.57	.16
Prescence of PVD (n, %)	26, 40.0%	.94
Volume of vitreous sample (mL) mean ± SD	2.1 ± 0.2	
< 2 mL (n, %)	7, 10.8%	
= 2 mL (n, %)	31, 47.7%	
> 2 mL (n, %)	27, 41.5%	
Liquefication of vitreous (n, %)	16, 24.6%	.0039
Prescence of retinal lattice degeneration	7, 10.8%	.19

SD = standard deviation; PPV = pars plana vitrectomy; BCVA = best-corrected visual acuity; PVD = posterior vitreous detachment

color fundus photograph with a digital fundus camera, optical biometry (IOLMaster; Carl Zeiss Meditec, Dublin, CA), and fluorescein angiography (FA) (Spectralis OCT+HRA; Heidelberg Engineering, Heidelberg, Germany) if secondary macular ERM was suspected. Optical coherence tomography (OCT) images were obtained by spectral-domain OCT (Carl Zeiss Meditec, Dublin, CA). BCVA, axial length (AL), presence of posterior vitreous detachment (PVD; defined as the presence of a Weiss ring and visible posterior vitreous cortex under the slit-lamp biocular biomicroscopy examination by the same surgical doctor[10]), baseline OCT characteristics, sex, age, and refraction were recorded as baseline data.

Three-Port PPV

All patients underwent a surgical procedure under local anesthesia. Phacoemulsification surgery was performed before vitrectomy in case of necessary determined by the surgeon before surgery. The Alcon CONSTELLATION Vision System (Alcon Laboratories, Fort Worth, TX) was used for vitrectomy in all cases with the Merlin wide-angle viewing system (Volk Optical, Mentor, OH). The standard infusion sclerotomy port was created with the trocar first, with the infusion line connected to the Constellation with the air-fluid exchange button turned on and initial air pressure setting as 33 mm Hg to 35 mm Hg and was positioned near the site of infusion sclerotomy and in the vitreous right after the sclerotomy was performed. The air pressure was adjusted in case of hypotony when the first instrument sclerotomy was performed. If hypotony was still present, the canula plug was applied to the first sclerotomy port before the other sclerotomy was made. The 23-gauge vitrectomy handpiece was directly connected to a 5-mL syringe. The surgeon controlled the position of the vitrectomy handpiece to harvest

vitreous beneath the air bubble inside the vitreous while the assistant manually aspirated the vitreous into the syringe slowly and constantly. When the vitreous sample in the syringe was 2 mL or more, as required by the protocol of the proteomic analysis of vitreous from patients with MH and ERM mentioned above, the fluid infusion was turned on, the posterior vitreous detachment was created, if necessary, and a complete PPV was performed. Vitreous liquefaction was defined as there was significant fluid observed escaping from the sclerotomy port when the infusion sclerotomy was performed. The vitreous sample was stored in liquid nitrogen as soon as the sample was collected for further proteomic analysis.

Follow-Up

Visits were scheduled at 1, 2, 7, 14, and 30 days, as well as 3 months after the initial surgery. The examination included BCVA, dilated fundus examination, color fundus photography, and OCT. BCVA at 30 days and occurrence of any surgery-related complication within the first 3 months were recorded. The potential complications of vitrectomy included endophthalmitis, retinal detachment, vitreous hemorrhage, hypotony, and secondary glaucoma.

Statistical Analysis

Statistical analysis was performed using R version 3.20 (http://www.R-project.org). Patient characteristics were retrieved from their medical charts and recorded in Epidata Entry Client version 2.0.3.15 (http://epidata.dk). BCVA results were converted to a logMAR value for statistical analysis. Mean and standard deviation (SD) were calculated for continuous variables with normal distribution. Median with quartiles was calculated for continuous variables with a non-normal distribution. The *t*-test or Mann-Whitney U test was carried out for continuous variables. The Chi-square test or Fisher's exact test was carried out for discrete data. To explore the changes in BCVA before and after vitreous biopsy, the Wilcoxon signed-rank test was carried out to compare VA at follow-up to that at baseline. To explore the potential factors that may influence the volume of vitreous sample that acquired during surgery, we divided the volume of vitreous sample into two categories: sufficient sample (sample volume ≥ 2 mL) and insufficient sample (volume < 2 mL). Several factors including the presence of PVD, AL, refraction, age, and presence of vitreous liquefaction found during surgery were compared between eyes with sufficient samples and those with insufficient samples (Table 1). Variables were further enrolled in a binary backward stepwise logistic regression model. One variable was included or excluded from the model each time by comparing the Akaike information criterion (AIC) value, and the model that had the lowest AIC was chosen.

RESULTS

In total, 65 eyes of 65 patients who met the criteria mentioned earlier were analyzed. The mean age of patients was 62.9 years ± 8.4 years (range: 35 years to 85 years) at diagnosis. There were 18 male and 47 female patients. Patients with a diagnosis of ERM had a higher rate of PVD (90%, 18/20) compared with patients with a diagnosis of MH (17.1%, 8/45; $P < .001$). In patients with MH, seven had Weiss rings found before the vitrectomy; however, there were three patients who were confirmed during vitrectomy to not have a PVD. There were 51 patients who underwent phacoemulsification cataract extraction combined with PPV. There were 20 patients with ERM and 45 patients with MH. Air tamponade were used in cases if necessary. All MHs were closed at 1-month follow-up. Additionally, at 1-month follow-up, 31 patients had VA improvement of more than 3 lines, 34 patients had VA improvement of less than 3 lines, and no patient had a decrease in VA. There were no significant VA changes at 1-month follow-up compared with baseline VA ($P = .14$). Details characteristics of patients are listed in Table 1.

Complications of Vitreous Biopsy

Incidence of a retinal break in the operation: There were seven patients with retinal lattice degeneration founded before the operation. Among them, there was one patient who had a peripheral retinal break and was treated with photocoagulation during the operation (1.5%). There was no patient with iatrogenic rhegmatogenous retinal detachment either during the operation or at 3-month follow-up. The patient who had a peripheral retinal break during the operation was a 64-year-old female with a diagnosis of macular ERM. She was found to have PVD before the operation, and vitreous liquefaction was found during the operation. Neither patient developed endophthalmitis, vitreous hemorrhage, retinal detachment, secondary glaucoma, or hypotony at 3-month follow-up.

Volume of vitreous sample harvest during the biopsy: The mean vitreous sample volume was 2.1 mL ± 0.2 mL. There were seven patients whose vitreous samples were less than 2 mL during the vitreous biopsy. Based on a binary backward stepwise logistic regression model, presence of vitreous liquefaction found during the biopsy was related to insufficient vitreous sample, whereas patients' age, combination of phacoemulsification cataract extraction and intra-

ocular lens implantation, ocular AL, VA, presence of PVD, and presence of peripheral retinal lattice degeneration were not related to insufficient vitreous samples (P = .003; AIC = 34.93). The rate of insufficient vitreous sample that may occur during the vitreous biopsy under air infusion in patients with vitreous liquefication was 28.8% (odds ratio 95% confidence interval, 4.3% to 57.68%).

DISCUSSION

In this study, we retrospectively investigated the incidence of complication and vitreous sample volume of a small group of patients without vitreous inflammation treated with vitrectomy under air infusion.

The mean volume of undiluted vitreous sample harvested from the biopsy was 2.1 mL ± 0.2 mL. There was only one patient who had a peripheral retinal break during the vitrectomy biopsy procedure, whereas we did not observe any cases of retinal detachment, endophthalmitis, hypotony, or secondary glaucoma as mentioned in previous reports on vitreous biopsy.[2,4,11,12] This suggests that vitreous biopsy with vitrectomy under air is a safe and effective procedure in patients with ERM or MH. A larger sample with a longer observation period and variety of diseases with inflammation involving the vitreous is still required to confirm our hypothesis. The vitreous biopsy with vitrectomy under air infusion with 23-gauge instruments has advantages, including the ability to harvest both core and peripheral vitreous samples with a wider field of view, a better visualization of the vitreous base, and a higher surface tension at the air-vitreous interface, as found in previous reports with both 20-gauge and 25-gauge instruments.[7-9]

The improvement of VA can be observed in patients with ERM or MH undergoing vitrectomy.[1-3] We found a similar rate of VA improvement or stabilization in our series of ERM and MH patients, which suggests that the vitrectomy procedure combined with biopsy is safe and effective to treat ERM and MH. The incidence rate of a retinal break during vitrectomy was reported as 0% to 15.8%.[13-21] The sclerotomy-related retinal breaks,[20] tears related to the incarceration of vitreous in the sclerotomy[14,18] or to the introduction of PVD,[14,16] were common types of intraoperative retinal breaks. In the current study, we reported one patient with a retinal tear in the peripheral retinal lattice degeneration found during the biopsy. This patient had a PVD at the time of vitrectomy. Previous reports found retinal breaks developing more frequently in eyes in which a PVD was induced during vitrectomy compared with eyes in which a PVD was present at the time of PPV in patients with macular ERM or MH.[13,15,16,22] The strategy to harvest vitreous under air infusion should begin with cutting the anterior vitreous, then cutting the core vitreous just behind the air bubble, then cutting the posterior vitreous underneath the air bubble if more sample is required. The shaving of peripheral vitreous cortex around the air bubble should be preserved with caution. In most conditions, when the sample volume meets the requirement, inducing PVD or shaving the residual peripheral vitreous body should be performed with fluid infusion turned on (Figure 1). Since the air bubble can help to stabilize the vitreous body in the procedure and peripheral vitreous body was shaved with fluid infusion, it seems that the biopsy procedure alone is not related to retinal tear.

The liquefication of vitreous was the factor we found to be related to the insufficient vitreous sample. The vitreous gel undergoes age-related liquefaction.[23,24] We performed the vitrectomy with 23-gauge non-valved instruments. The fluid escaping from the infusion sclerotomy may cause both hypotony and an insufficient vitreous sample. It is difficult to make the other two sclerotomies with hypotony present. Furthermore, hypotony may cause the air bubble to enter the vitreous cavity before starting the cutter, which blurs the view. Additionally, the air flow may damage the retina contralateral to the inject site.[25,26] The liquefication of vitreous is hard to predict before the vitrectomy. It is better to prevent the hypotony by using a valved canula or by putting the air infusion near the infusion sclerotomy site and lessening the interval between the sclerotomy and putting the line into it. If vitreous liquefication happens, it is better to up-regulate the air-fluid exchange air pressure temporarily to increase the tension inside the eyeball. By doing this, it is much easier to finish the other sclerotomy. Cannula plug should be applied if low tension occurs after the first sclerotomy is performed with air infusion on. To harvest the residual vitreous, the vitrectomy cutter should start right behind the air bubble, and the wide-angle view system should be adjusted to obtain a better view under air. Special attention should be paid to the contralateral side of peripheral retina to the infusion port. Furthermore, the sterile tube in the aspiration line of the vitrectomy machine held by the assistant should adjust the aspiration speed according to the intraocular pressure as mentioned in a previous study.[12] A 5-mL syringe is better for both harvesting more vitreous sample and keeping a sustained aspiration speed compared with a 2-mL syringe. Additionally, the 5-mL syringe has clearer scale view and is easier to control the aspiration speed compared with a 10-mL syringe.

As previously reported, the air can fog the intraocular lens and compromise the view under air in the condition of the pseudophakic eye with a disrupted posterior capsule.[8,9,27,28] It is better to leave the posterior capsule alone until the vitrectomy is finished. In cases where the posterior capsule is already broken, soft-tipped cannulas may help clear the fog.

This study was part of a proteomic analysis of the vitreous of patients with MH or ERM. In this paper, we focused only on the method to harvest vitreous with the 2-mL volume required to carry out the proteomic analysis of vitreous. The pathology results of the vitreous samples were included in another manuscript. It was easy to harvest more than 2 mL of vitreous using other tests, including flow cytometry and polymerase chain reaction (PCR). We also tried to harvest vitreous samples in cases of suspected toxocariasis and tuberculosis using enzyme-linked immunosorbent assay and PCR; however, those cases are not reported here. Further work to test the safety of vitreous biopsy under air in patients with chronic inflammation or tumor should be considered if a high amount of undiluted vitreous sample is required. A controlled study with a pathologic result of the vitreous sample may be required to test the hypothesis regarding whether the 23-gauge instruments are better for harvesting the vitreous sample under air compared to 25- or 27-gauge instruments.

In summary, non-valved 23-gauge vitrectomy under air infusion is a safe and effective maneuver to harvest undiluted vitreous in patients with ERM and MH for proteomic analysis. Caution should be taken when considering patients with significant inflammation involving the vitreous.

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