• Clinical Research •

Pars plana vitrectomy for retinal detachment using perfluoro-n-octane as intraoperative tamponade: a multicenter, randomized, non-inferiority trial

Xin Shi[1], *Wei-Jun Wang*[1], *Ying Fan*[1], *Hai-Yun Liu*[1], *Hong Wang*[1], *Yu-Hui Chen*[2], *Ao Rong*[3], *Zhi-Feng Wu*[4], *Xun Xu*[1], *Kun Liu*[1]

[1]Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, National Clinical Research Center for Eye Diseases, Shanghai Key Laboratory of Ocular Fundus Diseases, Shanghai Engineering Center for Visual Science and Photomedicine, Shanghai Engineering Center for Precise Diagnosis and Treatment of Eye Diseases, Shanghai 200085, China

[2]Shanghai Jieshi Medical Technology Co. Ltd., Shanghai 201201, China

[3]Department of Ophthalmology, Tongji Hospital, School of Medicine, Tongji University, Shanghai 200065, China

[4]Department of Ophthalmology, Wuxi No.2 People's Hospital (Jiangnan University Medical Center, JUMC), Wuxi 214002, Jiangsu Province, China

Correspondence to: Kun Liu. Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, No.85, Wujin Road, Hongkou District, Shanghai 200085, China. drliukun@sjtu.edu.cn.

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Abstract

● **AIM:** To evaluate the efficacy and safety of perfluoro-n-octane (PFO) for ophthalmic surgery versus F-Octane as an intraoperative tamponade in pars plana vitrectomy (PPV) in management of retinal detachment.

● **METHODS:** This multicenter, prospective, randomized, double-masked, parallel-controlled, non-inferiority trial was conducted in three ophthalmology clinical centers in China. Patients with retinal detachment, who were eligible for PPV were consecutively enrolled. Participants were assigned to PFO for ophthalmic surgery or F-Octane for intraocular tamponade in a 1:1 ratio. Best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurement, and dilated fundus examination were performed preoperatively and at 1, 7±1, 28±3d postoperatively. The primary outcome was complete retinal reattachment rate at postoperative day one. The non-inferiority margin was set at 9.8%. The secondary outcomes included intraoperative retinal reattachment rate, and mean changes in IOP and BCVA from baseline to 1, 7±1, 28±3d postoperatively, respectively. Safety analyses were presented for all randomly assigned participates in this study.

● **RESULTS:** Totally 124 eligible patients completed the study between Mar. 14, 2016 and Jun. 7, 2017. Sixty of them were randomly assigned to the PFO for ophthalmic surgery group, and 64 were assigned to the F-Octane group. Baseline characteristics were comparable between the two groups. Both groups achieved 100% retinal reattachment at postoperative day one (difference 0, 95%CI: -6.21% to 5.75%, P=1). The pre-defined noninferiority criterion was met. No significant difference was observed in intraoperative retinal reattachment rate (difference 1.77%, P=0.61), mean changes in IOP (difference 0.36, -0.09, 2.22 mm Hg at 1, 7±1, 28±3d postoperatively, with all P>0.05) and BCVA (difference 0.04, -0.02, 0.06 logMAR at 1, 7±1, 28±3d postoperatively, all P>0.05) between the two groups. No apparent adverse events related to the utilization of PFO were reported.

● **CONCLUSION:** In patients with retinal detachment undergoing PPV, PFO for ophthalmic surgery is non-inferior to F-Octane as an intraocular tamponade, and both are safe and well-tolerated.

● **KEYWORDS:** perfluoro-n-octane; vitreoretinal surgery; intraocular tamponade; ophthalmic surgery; retinal detachment

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INTRODUCTION

Pars plana vitrectomy (PPV) is one of the most prevalent ophthalmic surgical procedures. The advancement

of vitrectomy systems, coupled with the integration of intraocular devices such as triamcinolone acetonide, vital dyes and intraocular tamponades, has substantially enhanced the optimization of this surgical procedure[1]. In particular, intraocular tamponade perfluorocarbon fluids (PFCLs) as vitreous substitutes have drastically altered the management and prognosis of vitreoretinal diseases[2-4].

Perfluoro-n-octane (C_8F_{18}, PFO) is among the most commonly used PFCLs, since first introduction in vitreoretinal surgeries in 1980s[5], these compund have been effectively employed for intraoperative manipulation. PFO is characterized by a specific gravity of 1.75, low viscosity, a distinct interface, a high vapor pressure, and is obtainable in a highly purified form. The high vapor pressure is especially advantageous, as this allows for a thin layer of heavy liquid to remain on the retinal surface during the fluid-air exchange. A layer of PFO will evaporate quickly as air flushes through the eye. The density of these compounds makes them advantageous for various vitreoretinal surgical procedures, including repositioning retinal breaks, removing subretinal fluid, and unfolding and stabilizing the detached retina[6]. The high interfacial tension of PFO restricts the potential passage through retinal breaks, whereas the optical clarity facilitates intraoperative visualization for operations[7].

Recently, a novel fluorinated alkane methodology was employed to develop PFO for ophthalmic surgery (Jieshi Medical Technology Co. Ltd., Shanghai, China), which eliminates minute quantities of dangerous hydrogen-containing impurities (Patent Nos. CN105693464A; CN103936547B). Published preclinical studies have demonstrated that PFO was well-tolerated in rabbits as short-term residue[8]. On the basis of these, this study was initiated to evaluated the efficiency and safety of PFO for ophthalmic surgery versus F-Octane (FLUORON Gmbh, Neu-Ulm, Germany) when utilized as temporary fillers in vitreoretinal surgery. This article presented an overview of this multicenter, prospective, randomized, double-masked, parallel-controlled, non-inferiority trial.

SUBJECTS AND METHODS

Ethical Approval This study was approved respectively by the Ethics Committees of Shanghai General Hospital (Approval No.2016-43), Shanghai Tongji Hospital (Approval No.304), and Wuxi Second People's Hospital (Approval No.2017001), and adhered to the tenets of the Declaration of Helsinki. All participant or a legal representative reviewed and signed written approved informed consent documents. This trial was filed with the medical products administrations of the Shanghai government, recordation number: 20160074.

Participants The inclusion criteria were 1) 18y and older, regardless of gender; 2) clinical manifestations of retinal detachment; 3) ability to sign a written informed consent and comply with study assessments for the full duration of the study.

The exclusion criteria were 1) retinopathy in both eyes, necessitated concurrent procedures; 2) significant media opacity (severe cataract, cornea scar, *etc*); 3) serious systemic diseases, including cardiovascular disease or myocardial infarction within 12mo prior to enrollment; severe neurological disease; severe infection; active disseminated vascular intravascular coagulation; 4) participated in any other clinical trial within the prior 1mo; 5) pregnancy or lactation; 6) psychiatric disease or any other condition likely to interfere with study participation or with the ability to complete the trial by the judgment of the investigator.

Randomization and Masking Stratified block randomization was utilized to allocate eligible paticipants randomly to either PFO for ophthalmic surgery (PFOa) or F-Octane (PFOb) in a 1:1 ratio by the center. Random number tables were generated using SAS 9.1 statistical software (SAS Institute, Cary, NC, USA) by an independent computer operator. The study was double-masked to prevent performance and detection bias. Treatment assignment was concealed from the patients, optometrists, clinical investigators, and evaluating investigators. Random assignment was carried out by drawing a sealed, opaque, sequentially numbered envelope at each center, ensuring that neither clinicians nor participants knew the treatment allocation. Investigators at each center assigned random numbers to the subjects according to the order of enrollment, opened and sealed the corresponding random envelopes according to the random numbers, and assigned the corresponding devices for the trial according to the device numbers of the random envelopes. The unmasked investigator hands the study product to the surgical operator's assistant based on the random envelope assignment, and the unmasked assistant drew the study product into a syringe and handed it to the surgical operator. Unmasking was only performed after all the patients had completed treatment. If patients experienced any serious adverse events (SAEs) necessitating disclosure of drug usage, they were unmasked and the sponsor notified; following which, they were withdrawn from the study.

Treatments All patients underwent a standard three-port PPV using 23-gauge instruments, performed by experienced vitreoretinal surgeons. Depending on the condition of the retina, pars plana lensectomy, membrane segmentation, delamination, and peeling were conducted; fibrous membranes were removed as extensively as possible to relieve traction on the retina. PFO was then injected slowly through a 25- or 27-gauge blunt needle to fill the vitreous cavity with a single bubble, avoiding the optic disc and macula to prevent retinal stress and dispersion of the PFO. Laser photocoagulation was applied around the retinal breaks. Upon completion of the

surgery, heavy liquid was removed and exchanged by balanced salt solution, air, sulfur hexafluoride (SF_6), or silicone oil, and the sclerotomy sites were securely sutured.

Assessments Participants were followed up at days 1, 7±1, and 28±3 postoperative for ophthalmological examinations, including slit-lamp examinations, best-corrected visual acuity (BCVA) measurement, IOP measurement, dilated fundus examination and reporting of any adverse event (AE), following standard clinical practice.

BCVA was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart assessed at a starting distance of 4 m. Letters were converted to the logarithm of the minimum angle of resolution (logMAR) units for statistical analysis[9]. For off-chart BCVA measurements, we adapted previously established scales to assign logMAR values, counting fingers was set to logMAR 1.9, hand motion to 2.3, and light perception to 2.7[10-11].

Outcomes The primary outcome was the retinal reattachment rate determined by slit lamp pre-test or indirect ophthalmoscopy or trifocal fundus examination on postoperative day 1. The retinal reattachment rate on postoperative day 1 was used as the primary efficacy evaluation index, and days 7±1 and 28±3 were analyzed and evaluated to assess the long-term efficacy of retinal reattachment surgery. Secondary outcomes included intraoperative retina reattachment rate, and the mean changes in IOP and BCVA from baseline to every visit.

Safety assessments were investigated in the safety set at each visit by noting any complications during or after the procedure, including ocular and non-ocular AEs and SAEs.

Statistical Analysis All statistical analyses were performed using SAS software version 9.1.

This clinical study employed the postoperative retinal reattachment rate as the basis for sample size estimation. Literature reports suggest that the retinal reattachment rate on day 1 after vitreoretinal surgery with the application of PFO is 93%[12]. Assuming a retinal reattachment rate on day 1 after surgery was 98% with the application of this trial product, the clinical investigators and statisticians consequently established a clinical non-inferiority margin of 9.8%. A sample size of 51 evaluable patients per arm allowed non-inferiority detection between two groups, with 80% power and at the 0.05 level of significance (one-sided). Assuming a 20% dropout rate, the study required randomization of 64 patients per arm (for a total of 128) to obtain 51 evaluable patients.

Non-inferiority is claimed if the lower bound of the 95% confidence interval (CI) of the treatment effect difference between the PFOa and PFOb groups in the primary outcome does not exceed -9.8%. Continuous variables were presented as means±standard deviations (SD), while categorical variables were presented as frequencies (percentages). For all variables, percentages in tables and text are of nonmissing data. Statistical analysis was performed using a two-independent-samples *t*-test for continuous data and Cochran-Mantel-Haenszel χ^2 test or Fisher's exact test for categorical data, as appropriate. Logistic regression using a binary logit model was employed to analyze the primary outcome, considering the central effect. The difference between the two groups was considerd statistically significant with a P-value<0.05.

Table 1 Baseline demographic, clinical characteristics of full analysis set *n*=124

Characteristics	PFOa group (*n*=60)	PFOb group (*n*=64)	*P*
Age (y)	56.37±10.05 (24–80)	55.23±11.66 (20–75)	0.56
Sex			0.22
Male	30/60 (50%)	39/64 (60.94%)	
Female	30/60 (50%)	25/64 (39.06%)	
Study eye			0.70
Right eye	33/60 (55%)	33/64 (51.56%)	
Left eye	27/60 (45%)	31/64 (48.44%)	
Mean BCVA (logMAR)[a]	1.31±0.85	1.31±0.86	0.99
IOP (mm Hg)	11.83±3.23	11.97±4.1	0.84
Intraocular tamponade			0.40
Silicone oil	34/43 (79.07%)	39/48 (81.25%)	
Sulfur hexafluoride	3/43 (6.98%)	4/48 (8.33%)	
Air	6/43 (13.95%)	5/48 (10.42%)	
PFO volume used (mL)	4.17±1.12	3.9±1.23	0.21[a]

PFO: Perfluoro-n-octane; PFOa: Perfluoro-n-octane for ophthalmic surgery; PFOb: F-Octane; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure. [a]Tested using ETDRS chart, and converted to logMAR.

RESULTS

Patient Disposition and Baseline Characteristics Between Mar. 14, 2016 and Jun. 7, 2017, 130 eligible patients at 3 centers were enrolled, 2 of whom withdrew before assignment; thus, 128 patients were ultimately randomized during the inclusion period. The consort flow chart and analysis sets can be seen in Figure 1. Three patients did not fulfil the inclusion criteria after random assignment, one patient was excluded after random assignment but before treatment. Therefore, 124 patients were included in the full analysis set, of which 60 patients were allocated to PFOa group and 64 were allocated to PFOb group.

Participant characteristics of the full analysis set are summarized in Table 1, and there was no substantial imbalance in the demographic or ocular characteristics of both treatment arms at baseline. The baseline BCVA were 1.31±0.85 and 1.31±0.86 logMAR, baseline IOP were 11.83±3.23 and 11.97±4.1 mm Hg in the PFOa and PFOb groups, respectively.

Efficacy Primary and secondary study outcomes in the full analysis set are shown in Table 2. Due to residual gas in the vitreous cavity, data at 1d were missing for two of 60 patients

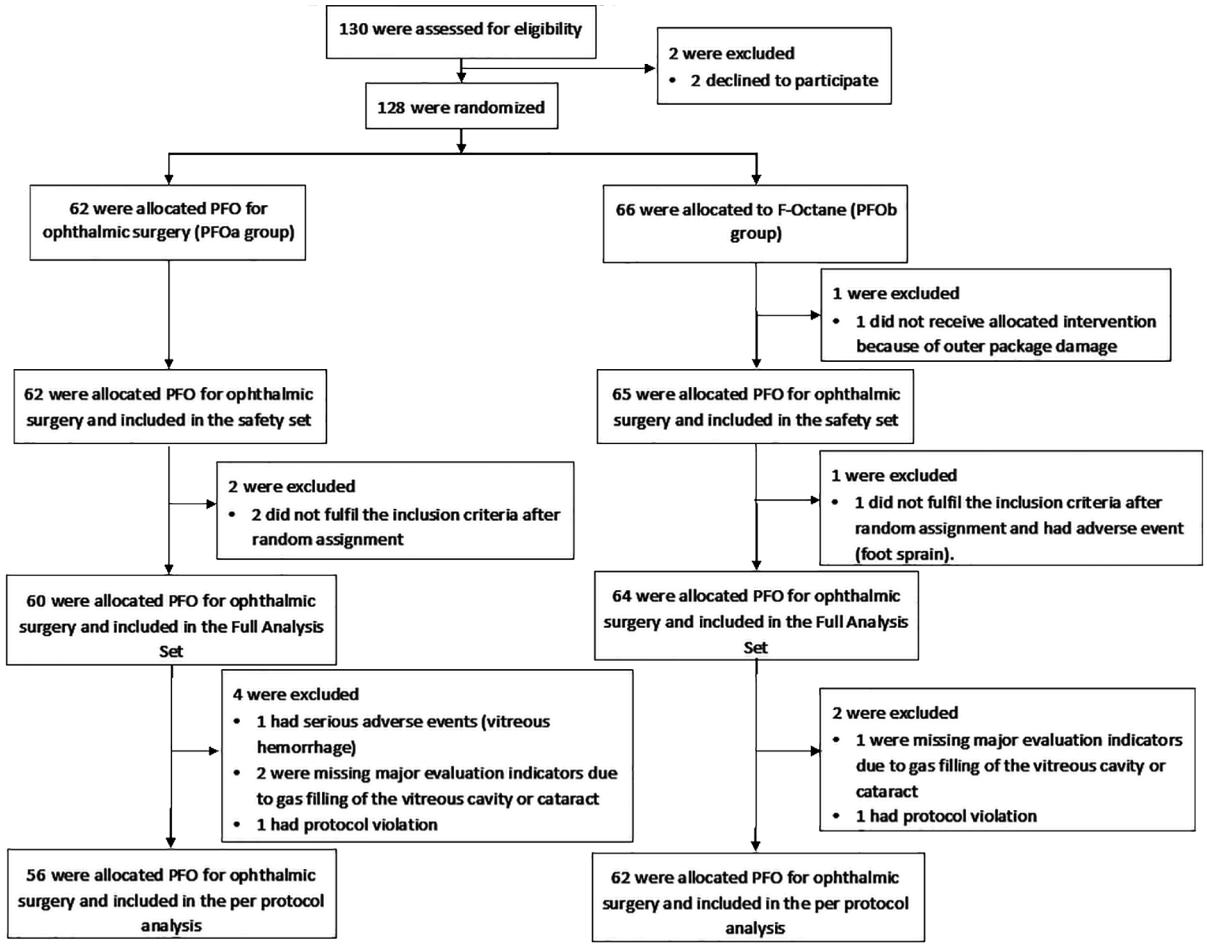

Figure 1 Study flowchart Flowcharts describing treatment allocation and patient disposition during the enrollment process in the study. PFO: Perfluoro-n-octane.

Table 2 Clinical outcomes in full analysis set *n*=124

Outcomes	PFOa (*n*=60)	PFOb (*n*=64)	Difference (95%CI)	*P*
Primary outcome				
Retina attached				
1d	58/58 (100%)	63/63 (100%)	0 (-6.21% to 5.75%)	1
7±1d	57/58 (98.28%)	61/63 (96.83%)	1.45% (-6.31% to 9.26%)	1
28±3d	59/59 (100%)	61/64 (95.31%)	4.69% (-2.16% to 12.90%)	0.27
Secondary outcomes				
Intraoperative retinal reattachment				0.61
Completely reattachment	58/60 (96.67%)	63/64 (98.44%)		
Partly or not reattachment	2/60 (3.33%)	1/64 (1.56%)		
IOP change from baseline (mm Hg)				
1d	2.01±8.86	1.65±7.67	0.36 (-2.60 to 3.34)	0.81
7±1d	6.37±9.34	6.46±10.01	-0.09 (-3.54 to 3.36)	0.96
28±3d	5.21±7.48	2.99±6.26	2.22 (-0.23 to 4.68)	0.08
BCVA change from baseline (logMAR)				
1d	0.25±1.00	0.21±1.13	0.04 (-0.34 to 0.43)	0.81
7±1d	-0.32±0.88	-0.30±1.03	-0.02 (-0.37 to 0.32)	0.89
28±3d	-0.55±0.80	-0.61±0.80	0.06 (-0.21 to 0.36)	0.62

PFOa: Perfluoro-n-octane for ophthalmic surgery; PFOb: F-Octane; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure.

in the PFOa group and one of 64 patients in the PFOb group; therefore, the primary analysis of favorable functional outcome (retinal attachment rate) was conducted in 58 patients in the PFOa group and 63 patients in the PFOb group. Complete retinal reattachment at postoperative day one was noted in 58 (100%) of 58 patients allocated PFOa compared with 63

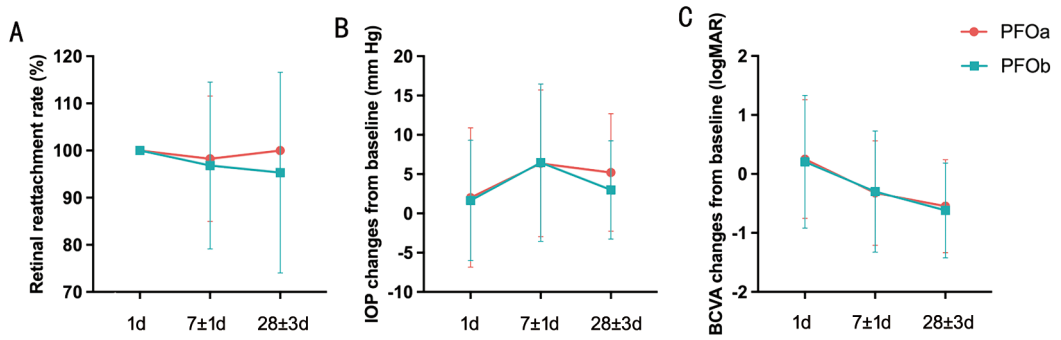

Figure 2 Primary and secondary outcomes on 1, 7±1, and 28±3d postoperatively A: The primary outcomes retinal reattachement rates in every visit; B, C: Secondary outcomes included mean changes in IOP (B) and BCVA (C) from baseline to 1, 7±1, and 28±3d postoperatively. Error bars denote standard deviations. All *P* values for interaction were >0.05. BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; PFOa: Perfluoro-n-octane for ophthalmic surgery; PFOb: F-Octane.

Table 3 Clinical outcomes in per protocol analysis *n*=118

Outcomes	PFOa (*n*=56)	PFOb (*n*=62)	Difference (95%CI)	*P*
Primary outcome				
Retina attached				
1d	56/56 (100%)	62/62 (100%)	0 (-6.42% to 5.83%)	1
7±1d	55/56 (98.21%)	60/62 (96.77%)	1.44% (-6.57% to 9.37%)	1
28±3d	56/56 (100%)	59/62 (95.16%)	4.84% (-2.32% to 13.29%)	0.25
Secondary outcomes				
Intraoperative retinal reattachment				0.60
Completely reattached	54/56 (96.43%)	61/62 (98.39%)		
Partly or not reattached	2/56 (3.57%)	1/62 (1.61%)		
IOP change from baseline (mm Hg)				
1d	2.01±8.86	1.65±7.67	0.36 (-2.60 to 3.34)	0.81
7±1d	6.37±9.34	6.46±10.01	-0.09 (-3.54 to 3.36)	0.96
28±3d	5.21±7.48	2.99±6.26	2.22 (-0.23 to 4.68)	0.08
BCVA change from baseline (logMAR)				
1d	0.23±1.03	0.21±1.10	0.02 (-0.37 to 0.41)	0.91
7±1d	-0.36±0.88	-0.32±0.99	-0.04 (-0.38 to 0.30)	0.81
28±3d	-0.54±0.80	-0.61±0.80	0.06 (-0.22 to 0.36)	0.64

PFOa: Perfluoro-n-octane for ophthalmic surgery; PFOb: F-Octane; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure.

(100%) of 63 patients allocated PFOb, with a difference of 0 (95%CI, -6.21%, 5.75%). The lower bound of the 95%CI of the treatment difference (-6.21%) was above the non-inferiority margin (-9.8%). The retinal reattachment rate on postoperative day 7±1 was 98.28% in the PFOa group and 96.83% in the PFOb group, with a difference of 1.45% (95%CI, -6.31%, 9.26%), and the retinal reattachment rate on postoperative day 28±3 was 100% in the PFOa group and 95.31% in the PFOb group, with a difference of 4.69% (95%CI, -2.16%, 12.90%), respectively (Figure 2A). The non-inferiority margin of -9.8% was crossed in all visits analyzed.

As for the secondary outcomes, the intraoperative retinal reattachment rate was analyzed, and completely retinal reattachment was achieved in 58 (96.67%) of 60 patients in the PFOa group, and 63 (98.44%) of 64 in the PFOb group (absolute difference 1.77%, *P*=0.61). Similarly, there was no statistically significant difference in the mean change in IOP and BVCA from baseline examined at postoperative days 1, 7±1 and 28±3 in patients of the PFOa and PFOb groups, respectively (Figure 2B, 2C). Mean differences of change in IOP between the two groups were 0.36 mm Hg at 1d, -0.09 mm Hg at 7±1d, and 2.22 mm Hg at 28±3d (all *P*>0.05). Likewise, mean differences of change in BCVA between two groups were 0.02 logMAR at 1d, -0.04 logMAR at 7±1d, 0.06 logMAR at 28±3d (all *P*>0.05).

Results of the per-protocol analysis were also presented in the Table 3. In the per-protocol analysis, the primary outcome retinal reattachment rate at postoperative day 1 was observed comparably often in both treatment groups (100%, separately, difference 0, 95%CI -6.42% to 5.92%, lower limit of 95%CI -12.4%, crossing the non-inferiority margin of -9.8%). Similarly, secondary outcome analysis demonstrated

Table 4 Mean IOPs and BCVA scores

Variations	Full analysis set (*n*=124)			Per protocol analysis (*n*=118)		
	PFOa (*n*=60)	PFOb (*n*=64)	*P*	PFOa (*n*=56)	PFOb (*n*=62)	*P*
IOP (mm Hg)						
1d	13.65±8.12	13.85±6.18	0.88	13.85±7.93	13.72±6.17	0.92
Range	4.6 to 39	3.4 to 29.8		-10.2 to 30.8	-12.7 to 24.7	
7±1d	18.69±9	18.41±9.78	0.87	18.2±8.64	18.43±9.79	0.89
Range	4.6 to 43.7	6.4 to 52.7		-8.7 to 35.4	-7.7 to 38.8	
28±3d	16.65±7.16	14.62±5.18	0.09	17.02±7.13	14.96±5.14	0.07
Range	7.7 to 42	3.2 to 32		-5.4 to 29.8	-14.5 to 20.4	
BCVA scores (logMAR)						
1d	1.56±0.78	1.52±0.78	0.78	1.56±0.54	1.52±0.52	0.81
Range	0.04 to 2.7	0.08 to 2.7		0.2 to 2.7	0.08 to 2.7	
7±1d	0.99±0.66	1.01±0.71	0.83	0.97±0.54	0.99±0.52	0.84
Range	-0.02 to 2.7	-0.1 to 2.7		0.1 to 2.7	-0.1 to 2.7	
28±3d	0.76±0.54	1.52±0.78	0.50	0.79±0.54	0.70±0.52	0.40
Range	0.04 to 2.7	-0.26 to 2.7		0.04 to 2.7	-0.26 to 2.7	

PFOa: Perfluoro-*n*-octane for ophthalmic surgery; PFOb: F-Octane; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure.

Table 5 Product property evaluation

Parameters	Full analysis set (*n*=124)			Per protocol analysis (*n*=118)		
	PFOa (*n*=60)	PFOb (*n*=64)	*P*	PFOa (*n*=56)	PFOb (*n*=62)	*P*
Retained PFO			1			1
Yes	0/60	0/64		0/56	0/62	
No	60/60 (100%)	64/64 (100%)		56/56 (100%)	62/62 (100%)	
Refractive qualification rate			0.31			0.24
Yes	39/60 (65%)	47/64 (73.44%)		35/56 (62.5%)	45/62 (72.58%)	
No	21/60 (35%)	17/64 (26.56%)		21/56 (37.5%)	17/62 (27.42%)	
Water solubility conformity rate			0.23			0.47
Yes	58/60 (96.67%)	64/64 (100%)		55/56 (98.21%)	62/62 (100%)	
No	2/60 (3.33%)	0/64		1/56 (1.79%)	0/62	
Fish-egg phenomenon[a]			0.29			0.36
Minor: fish-eggs <5	51/60 (85%)	53/64 (82.81%)		49/56 (87.5%)	51/62 (82.26%)	
Moderate: 5≤fish-eggs ≤20	8/60 (13.33%)	6/64 (9.38%)		6/56 (10.71%)	6/62 (9.68%)	
Severe: fish-eggs >20	1/60 (1.67%)	5/64 (7.81%)		1/56 (1.79%)	5/62 (8.06%)	

PFO: Perfluoro-n-octane; PFOa: Perfluoro-*n*-octane for ophthalmic surgery; PFOb: F-Octane. [a]Fish-egg phenomenon is the appearance of multiple small liquid globules that appear in the shape of fish eggs after intravitreal injection of FPO. High purity heavy liquids should be able to maintain the large liquid globules after injection.

equivalent results for both groups, with no significant difference in intraoperative retinal reattachment rate, IOP change from baseline, and BCVA change from baseline across visits, consistent with the results of the FAS analysis.

Table 4 presented the specific values for the mean IOP, and BCVA scores for both groups in the 3 follow-up visits. On the whole, the results were relatively balanced and not statistically significant for the two groups of patients, both in the full analysis set (FAS) and the per protocol analysis (all $P>0.05$).

The prespecified technical efficacy outcomes were demonstrated Table 5. In the clinical trial FAS, the residue-free rate was 100% in both the PFOa and PFOb groups; the refractive pass rate was 65% in the PFOa group and 73.44% in the PFOb group; the refractive qualification rate was 96.67% in the PFOa group and 100% in the PFOb group; and the incidence of serious fish-egg phenomenon, defined as more than 20 globules, was 1.67% in the PFOa group and 7.81% in the PFOb group. The lower refractive qualification rate was mainly due to the inconsistent assessment criteria in one center, which had no effect on the results. Overall, there was no statistically significant difference between the two groups in pre-defined technical efficacy outcomes (all $P>0.05$), thus confirming the equivalent technical efficacy of both PFOs.

Safety The distribution of AEs in the safety set was presented

Table 6 AEs and adverse reactions in the safety set *n*=127

Parameters	PFOa (*n*=62)		PFOb (*n*=65)		*P*
	No. of events	No. of patients	No. of events	No. of patients	
All AEs	165	62 (100%)	176	65 (100%)	1
SAEs	3	3 (4.84%)	3	3 (4.62%)	1
Drop out due to AEs	1	1 (1.61%)	1	1 (1.56)	1
AEs related to product	0	0	0	0	1
Ocular AEs of study eye					
Conjunctival congestion	57	57 (91.94%)	64	63 (96.92%)	
Eyelid edema	36	36 (58.06%)	37	37 (56.92%)	
Increased intraocular pressure[a]	21	20 (32.26%)	21	17 (26.15%)	
Corneal edema	17	17 (27.42%)	17	17 (26.15%)	
Conjunctival edema	10	10 (16.13%)	7	7 (10.77%)	
Glaucoma	9	7 (11.29%)	2	2 (3.08%)	
Retinal detachment	1	1 (1.61%)	2	2 (3.08%)	
Conjunctivitis	0	0	2	2 (3.08%)	
Retinal hemorrhage	1	1 (1.61%)	1	1 (1.54%)	
Vitreous hemorrhage	1	1 (1.61%)	1	1 (1.54%)	
Chorioretinal folds[b]	1	1 (1.61%)	0	0	
Retained PFO[c]	0	0	1	1 (1.54%)	
SAEs		3 (4.84%)		3 (4.62%)	1
Retinal detachment	1	1 (1.61%)	2	2 (3.08%)	
Vitreous hemorrhage	1	1 (1.61%)	1	1 (1.54%)	
Breast lump	1	1 (1.61%)	0	0	
Correlation judgment of AEs					0.66
Definitely related	3	2 (3.23%)	0	0	
Probably related	0	0	0	0	
Possibly related	1	1 (1.61%)	3	2 (3.08%)	
Unlikely to be related	67	29 (46.77%)	69	29 (44.63%)	
Definitely not related	94	42 (67.74%)	104	48 (73.85%)	

PFOa: Perfluoro-n-octane for ophthalmic surgery; PFOb: F-Octane; AE: Adverse event; SAE: Serious adverse event. [a]Elevated IOP but not enough to diagnose glaucoma; [b]Chorioretinal folds (CRFs) are undulations of the choroid and overlying Bruch's membrane, retinal pigment epithelium and neurosensory retina; [c]Retained PFO was noted in 28±3d.

in Table 6; altogether, 6 SAEs were reported throughout the trial, affecting 6 (4.72%) participants, with no statistically significant difference between two groups [3/62 (4.84%) in the PFOa group versus 3/65 (4.62%) in the PFOb group, *P*=1]. Of these, 4 cases were "definitely related" and 2 cases were "probably related" in the correlation judgment.

A total of 341 AEs were reported, affecting all 127 (100%) of participants, with no statistically significant differences between two groups (both 100%, *P*=1 for the comparison PFOa versus PFOb). Specifically, the vast majority of AEs were procedure-related and were mostly transient, mild in nature, or treatable. The most commonly reported ocular AEs were conjunctival congestion, eyelid edema, intraocular hypertension, corneal edema, conjunctival edema. There were 3 AEs affecting 2 participants (1.57%) reported which were deemed to be related to study treatments, with no statistically significant difference between groups. Both groups had one participant dropped out of the study due to AEs (foot sprain and vitreous hemorrhage).

DISCUSSION

The findings of this multicenter, randomized, non-inferiority trial demonstrated that PFO for ophthalmic surgery was non-inferior to F-Octane for intraocular tamponade in vitreoretinal surgery, and did not compromise patient safety.

No statistically significant difference was observed in all pre-defined outcomes between the two groups. The majority of participants (100% and 95.31% in the PFOa and PFOb groups respectively) achieved complete retinal reattachment at the final follow-up, align with the reported approximately 90% reattachment rate for first intervention[13-15]. For all pre-defined product property evaluation, both PFOs demonstrated remarkable properties. Following injection into the ocular fundus, due to their high purity, hydrophobicity and transparency, both PFOs were able to maintain the

large liquid globules and form a two-phase interface with the aqueous phase liquid without hindering the observation and manipulation. Upon completion of the procedure, both components could be easily and completely removed. There was no significant difference between the two groups for any of the assessd performance measures, demonstrating that the chemical characteristics of the two PFOs may be employed safely and effectively for fundus treatment.

Throughout the trial, most patients experienced a brief reduction in visual acuity on the first postoperative day, followed by a subsequent improvement. At 28±3d follow-up, the majority of patients maintained good vision. The mean BCVA were 1.31±0.85 and 1.31±0.86 logMAR at baseline, and improved -0.55±0.80 and -0.61±0.80 logMAR in the PFOa and PFOb groups respectively. Only a small percentage of patients (6/59, 10.17% in the PFOa group and 5/63, 7.94% in the PFOb group) experienced a loss of visual acuity ≥0.3 logMAR. The postoperative visual outcomes are influenced by various factors, and eventual visual acuity might have further improved over time[16]. Our results align with a large study involving 2413 patients, which reported a visual acuity change of -0.50 logMAR at 3mo postoperatively[17].

Elevated IOP is a common postoperative complication, influenced by various factors including oil tamponade, history of glaucoma or ocular hypertension, and topical corticosteroids as routine postoperative medications following surgery[18-19]. In our study, 27 patients in the experimental group and 25 patients in the control group reported an IOP over 21 mm Hg of all follow-ups; however, the number of patients with IOP spikes (defined as an IOP over 30 mm Hg) were only 9 cases in both groups, respectively. The highest IOP measured was 52.7 mm Hg in control group at visit 7±1d. In particular, we focused the IOP data on the postoperative day one. In our study, 18.11% of patients reported an IOP exceeding 21 mm Hg. Specifically, in the PFOa group, 20.9% experienced elevated IOP, while in the PFOb group, the proportion was 15.4%, and there were no statistically significant differences between the groups. These findings are consistent with similar large-scale retrospective investigations. For example, the study by Patel *et al*[20], involving 418 cases, reported a 16.5% incidence of elevated IOP, and Arikan Yorgun *et al*'s[21] study, based on 306 cases, showed that 15%–25% of patients showed elevated IOP. None of these participants reported severe pain, or were found to have hypotony or epithelial defects. Topical ocular antihypertensive medications were added for 20 patients in the control group and 23 in the experimental group, and by the time of the final follow-up, only a small proportion of participants had hyper IOP exceeding 21 mm Hg (10/61, 16.3% in the trial group and 8/64, 12.5% in the control group).

Both types of PFO proved to be highly safe. The vast majority of AEs were non-serious and already known to be attributable to the surgical procedures, including conjunctival congestion, eyelid edema, intraocular hypertension, corneal edema, and conjunctival edema. Only a mininal number of participants (the highest for any of the following events being about 4%) experiencing AEs potentially related to the use of PFO, including chorioretinal folds, glaucoma, corneal edema, conjunctivital edema, retained PFO and mixed congestion. These potential AEs were identified and documented prior to the commencement of the trial. At each visit, patients were questioned about their condition and evaluated by experienced ophthalmologists to determine whether any of these AEs had occurred, and management changes were made accordingly. None of SAEs reported, however, was attributed by the investigators as clearly being the result of the use of PFO.

PFO was widely acknowledged for its biological and biochemical inertness, making it widely accepted as a safe intraocular tamponade extensively used in ophthalmic procedures[22-23]. Notably, PFO has augmented the enhancement of surgical management of vitreoretinal disorders. Intraoperative application of PFO has been documented for retinal detachment, proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), ocular traumas, and removal of foreign bodies[24]. However, since 2013, cases of ocular toxicity mostly characterized by retinal necrosis, retinal vascular occlusion after the use of the commercially available AlaOcta PFO (Alamedics, Germany) had been reported in Spain and throughout Europe[18,25-27]. Retrospectively, these SAEs associated with individual batches were caused by effects from reactive underfluorinated impurities, especially of incompletely fluorinated by-products, which were unavoidable by-products of their synthesis and should be eliminated by thorough purification[7,28-29]. The emergence of these issues had sparked discourse concerning premarket medical device safety testing, as the manufacturer asserted that the security of the raw material and product were tested through *in vitro* cytotoxicity testing of the aqueous extract according to International Organization for Standardization (ISO) 10993-5 (2009). Nevertheless, some researchers argued that based on the norms and recommendations of ISO 10993-5 (2009), the only reliable method to detect any potential cytotoxicity of PFCLs is by direct contact, not liquid extracts. Since testing of liquid extracts may not detect toxic impurities insoluble in water due to the incompatibility of PFCLs with aqueous solutions, which may lead to false negative results[30]. Moreover, some scholars raised questions regarding the validity of cytotoxicity test methods currently employed to certify the safety of PFO lots, and proposed new cytotoxicity test methods for volatile substances[31].

Completely purified and characterized PFCL used as an ocular endotamponade were still safe devices. As a valuable tool for vitreoretinal specialists, PFCLs have demonstrated a beneficial effect in draining subretinal fluid and providing an excellent tamponade effect, particularly in inferior or posterior retinal detachments, compared to gas or silicone oil[22]. In a recent survey of retinal specialists conducted by the American Society of Retina Specialists, 11% of American respondents indicated that they drain fluid use PFCLs routinely, in contrast, PCFLs were used routinely by 43% of international respondents[3]. Consequently, the clinical need for PFCLs has therefore prompted production techniques improvement to purification. In addition, a coordinated effort must be made between researchers, clinicians, companies and health authorities to establish strict standards regulating manufacturing, purification and biosafety control requirements[30,32].

There are some limitations in our study. Due to the restricted follow-up duration, the identification of certain outcomes might be constrained, such as the long-term results of retina reattachment[33], eventual visual acuity after removal of the silicone oil tamponade, and the prognosis of patients with high IOP. Moreover, incorporating examinations like optical coherence tomography and electroretinogram would help us in a more comprehensive evaluation of the retinal structure and function. This study focused on evaluating PFO's safety and efficacy in rhegmatogenous retinal detachment cases, limiting our understanding of its broader applications in various retinal detachment conditions. In future studies, it would be ideal to extend the monitoring period, include necessary examinations, and enroll patients with different types of retinal detachment.

In summary, this clinical trial showed that using PFO for ophthalmic surgery is as effective as F-Octane in patients having vitreoretinal surgery, with similar function and safety outcomes, providing a compelling rationale to support PFO for ophthalmic surgery as a surgical tamponade of choice for ophthalmologists.

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