

COHORT SAFETY AND EFFICACY STUDY OF SILURON2000 EMULSIFICATION-RESISTANT SILICONE OIL AND F4H5 IN THE TREATMENT OF FULL-THICKNESS MACULAR HOLE

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Purpose: To evaluate safety and efficacy of using Siluron2000 silicone oil in the treatment of full-thickness macular hole by comparing its propensity to emulsify with emulsification of the “gold standard” Siluron5000, and to assess safety and efficacy of F4H5 (perfluorobutylpentane) in removing emulsified oil droplets from the eye.

Methods: A single-center, randomized controlled parallel group trial in 72 patients undergoing vitrectomy for treatment of full-thickness macular hole. The study comprises four treatment groups. First, the total patient group was divided into 2 study arms of 36 patients each, receiving either Siluron2000 or Siluron5000 after vitrectomy with a 3-month follow-up after vitrectomy. Second, F4H5 was used during oil removal in half of the patients in each study arm (18 patients within each study arm) with follow-up at 6 weeks after oil removal. Oil droplets were counted within the removed oil; residual emulsification bubbles were quantified using ultrasound imaging.

Results: Safety and efficacy of the oils were comparable. Injection and removal time of Siluron2000 oil was significantly less than that of Siluron5000 oil. Patients treated with F4H5 had borderline significantly less emulsification droplets than those not treated with F4H5.

Conclusion: Siluron2000 silicone oil seems to be equally safe and effective as Siluron5000 oil but allows for better handling with the potential of reducing procedure time. The application of F4H5 seems to be safe and effective in reducing residual emulsification.

RETINA 35:2558–2566, 2015

Silicone oils are chemically inert substances that have been used to act as internal tamponades in vitreoretinal surgery procedures for more than 40 years now.^{1,2} Their use can be adopted in difficult cases of

retinal detachment such as those complicated with proliferative vitreoretinopathy, giant retinal tears, and penetrating ocular trauma but can also be used to treat full-thickness macular hole (FTMH).^{3–12} All types of silicone oils, “conventional” or “heavy,” should be removed from the eye in a second time after 3 months but do not demand any postoperative positioning. This type of treatment is able to achieve excellent visual results.

However, there are several disadvantages of using silicone oil. First, a second surgery is required to remove the oil from the eye. Intraocularly, silicone oils can emulsify, whereby the oil disperses with formation of small oil droplets, which can entail unwanted clinical manifestations,^{13–15} including glaucoma,^{16,17} inflammation and formation of fibrosis, and proliferative vitreoretinopathy¹⁸ with possibility of redetachment of the retina.^{19,20}

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This study was funded in part by an independent scientific grant supported by Fluoron.

P. Stalmans receives grant support from Bausch + Lomb, lecture fees from DORC—Dutch Ophthalmic Research Center BV and ThromboGenics NV, and is a consultant for Alcon. None of the remaining authors have any financial/conflicting interests to disclose.

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Emulsification of silicone oils is a multifactorial process influenced by the physicochemical properties of the oil, such as shear viscosity and extensional viscosity,^{21–24} and the interfacial tension^{25,26} in situ, created at the interface between the oil and the residual vitreous fluids. Consequently, it is clear that different types of silicone oils vary in their propensity to emulsify. Moreover, the presence of physiologic intraocular protein surfactants^{21,22,27,28} also plays an important role in initiating emulsification. The same applies to movements the eye is subjected to²⁹ and the use of certain intraocular instruments during vitreoretinal surgery.^{21,27,30,31}

The first and most obvious parameter having an influence on the onset of silicone oil emulsification is viscosity. The extent and susceptibility to emulsification increases with decreasing the oil's shear viscosity.^{21,22,32} Increasing its extensional viscosity, by adding very long-chain molecules to silicone oils with lower shear viscosity, reduces the mixtures' tendency to emulsify.²³ After exploring interindividual variations in onset of emulsification, it was discovered that lowering the interfacial tension between liquids in the eye renders the oil more prone to emulsification.³⁰ Intraocular phospholipids or proteins, in the form of erythrocyte membranes, lymphocytes, or plasma lipoproteins such as apolipoproteins, are able to lower interfacial tension inside the eye and can thereby enhance emulsification when present in relatively high levels and dependent on the clinical condition of the patient's eye.^{21,22,27,28} Emulsification of oils has also been shown to increase with vigorous shaking.^{27,29} Research has shown that mechanical energy from intraocular instruments increases emulsification with greater power and duration of use of the instrument.³³ Emulsification can even be promoted by small amounts of remnants or detergents left behind on reusable instruments after routine cleaning procedures.³⁴ The use of an encircling band seems to induce a geometric alteration in the anatomy of the eye and can thereby reduce shearing forces and, thus, emulsification inside the eye.³¹ For the same reasons, less emulsification is observed with a more complete fill of silicone oil.³¹

Until now, indications for the use of silicone oil as a vitreoretinal tamponade have extended widely. In this study, patients with FTMH were selected because they tend to only show little variation in age. Full-thickness macular hole generally manifests in patients between the age of 55 years and 75 years, except in rare posttraumatic cases, which were excluded from this study.³² Retinal detachment occurs at different ages, which could have biased the study, because onset of emulsification could be age-related and this

study was conducted within a relatively small cohort of patients.

Macular holes are mostly treated using gas tamponade. However, excellent anatomical and functional outcomes are achieved in our center by treating FTMH using silicone oil as tamponade for a time period of 3 months,^{11,12} as well as in other centers.³⁵ The fixed period of time after which the oil is removed in cases of FTMH eliminates a major time-variable influencing development and onset of emulsification.

Since the appearance and increased use of smaller-gauge instruments, the choice between ease of oil handling (low-viscosity oils) versus its resistance to emulsify (high-viscosity oils) has proven to be a difficult issue. There is a widespread agreement that development of tamponade agents with increased resistance to emulsification, while still maintaining ease of injection into and removal from the vitreous cavity, are needed.^{23,24,36–38}

Until relatively recently, only 1,000-centistoke (cSt) (low-viscosity) and 5,000 cSt (high-viscosity) silicone oils were commercially available. Generally, 1,000 cSt oils provide surgical and technical advantages, such as easier injection and extraction in comparison with 5,000 cSt oils, but they have stronger tendencies to emulsify. For this reason, until now, the U.S. Food and Drug Administration has solely approved 5,000 cSt oils for use. For many years, development of 2,000 cSt silicone oils has been on the way. Siluron2000 and Siluron5000 are highly purified,³⁹ commercially available, silicone oils comprising 100% polydimethylsiloxane. Both products are manufactured by Fluoron GmbH. Both oils are CE-certified: Siluron5000 was approved in 2002 and Siluron2000 in 2008. Although they bear the same commercial name, Siluron, they are quite different products. Siluron2000 comprises a mixture of 5% polydimethylsiloxane, with a shear viscosity of 2,500,000 Pa, and 95% polydimethylsiloxane, with a shear viscosity of 1,000 Pa. Siluron5000 is normal silicone oil with a kinematic viscosity of 5,000 cSt. It is considered as the "gold standard."

The main aim of the study was to evaluate, through a randomized control trial, the safety and efficacy of the recently introduced Siluron2000 silicone oil compared with those of the gold standard Siluron5000. In vitro studies have already shown that emulsification of Siluron2000 is less than Siluron5000 because of the viscoelastic properties of Siluron2000.²³ Specifically, this study compared the ease of injection and removal and the propensity of the oils to emulsify in vivo using a human clinical trial. For the purpose of the trial, novel methods of quantifying emulsification were introduced. One of these methods involved the use of F4H5.

F4H5 (perfluorobutylpentane— $C_4F_9-C_5H_{11}$) is a semi-fluorinated alkane that can dissolve silicone oil. It has a similar structure to F6H8 (perfluorohexyloctane— $C_6F_{13}-C_8H_{17}$) but is more amphiphilic and a superior solvent for silicone oil. F6H8 is manufactured by Fluoron GmbH and is CE-certified. F4H5 is not yet CE-certified but is widely used in experimental environments including clinical studies.^{35,40,41} A secondary outcome of the study was to evaluate the safety and efficacy of the use of F4H5 in a randomized way, as compared with no F4H5 in silicone oil removal, and to explore whether the additional use of a solvent can more completely remove silicone oil from the eye.

Objectives

The primary objective of the study was to evaluate the safety and efficacy of the recently introduced Siluron2000 silicone oil compared with those of the industry's current gold standard Siluron5000 oil. Secondary objectives were to evaluate the safety and efficacy of the subsequent use of F4H5 compared with no use of F4H5.

Methods

Inclusion criteria were male or female patients who were older than 18 years, with FTMH requiring vitrectomy and silicone oil tamponade. Written informed consent was obtained from each patient before inclusion in the study in compliance with the International Convention on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice (ICH-GCP). Exclusion from the study was based on any previous vitrectomy surgery, nonidiopathic macular hole (e.g., posttraumatic macular hole), high myopia in the study eye, inability to give written consent in accordance with ICH-GCP requirements, aphakia, participation in an investigational drug study within the past 30 days, patients with a life expectancy of less than 6 months, patients with active uveitis, and pseudophakic patients with silicone implant lenses.

The group of 72 patients was randomized into 2 study arms of 36 patients each, either to the Siluron2000 or Siluron5000 group. F4H5 was used during oil removal in half of the patients in each study arm (18 patients within each study arm), creating 4 treatment groups:

1. Siluron2000 with subsequent F4H5
2. Siluron2000 without subsequent F4H5
3. Siluron5000 with subsequent F4H5
4. Siluron5000 without subsequent F4H5.

All patients underwent 23-gauge vitrectomy with application of Siluron2000 (the first study arm) or Siluron5000 silicone oil (the second study arm) with follow-up of 3 months after vitrectomy. Silicone oil was removed 3 months later using a 23-gauge extraction system and a fixed vacuum of 600 mmHg (DORC Associate). In half of the patients in each study arm, F4H5 was injected into the vitreous cavity after removal of the bulk of the silicone oil from the eye to dissolve any remaining oil droplets. After 3 minutes, the F4H5 fluid was completely removed from the eye using a back flush instrument with active aspiration.

The study data were monitored and analyzed by the Trial Coordination Center, Department of Epidemiology, University Medical Center Groningen, Groningen, the Netherlands.

For evaluation of efficacy, the following parameters were assessed:

1. Ease of injection and extraction reflected by the amount of time required to inject/extract the oils
2. Success rate of FTMH closure
3. Tendency for the oil to emulsify.

Safety was evaluated through assessment of visual acuity (using Early Treatment Diabetic Retinopathy Study charts), visual perimetry (using Goldmann perimetry testing), and color contrast sensitivity (through examination of the tritan axis to avoid measurement errors related to common color blindness). Intraocular pressure was assessed at each study visit to indicate the presence of a secondary glaucoma caused by emulsification. Ocular coherence tomography immediately after the first surgery and before oil removal 3 months later, carried out by a masked observer, was used to evaluate whether any epiretinal fibrosis was caused by silicone oil in the eye.¹⁸

Screening visits took place ± 7 days before vitrectomy. Safety of both Siluron2000 and F4H5 were assessed 6 weeks after the first surgery and 6 weeks after oil removal. Efficiency parameters were assessed after vitrectomy at Day 1, Week 2, Week 6, and Month 3 (1 day before oil removal), and also after oil removal at Day 1, Week 2, and Week 6.

Emulsification was evaluated (indicating postprocedural safety and efficacy) through the following:

1. Gonioscopy by an independent and experienced observer to record the number of emulsified drops remaining in the anterior chamber after removal of silicone oil from the eye.
2. B-scan ultrasound carried out by a masked observer, with digital measurement of the number of oil droplets visible in the vitreous cavity after

removal of silicone oil from the eye. Using methylcellulose as a contact gel, a B-scan ultrasound was performed using an Ellex Eye-Cubed 10-MHz B-Scan Probe, placing the probe on the sclera after instillation of a topical anesthetic drop. Evaluation of the emulsification of silicone oil in situ was performed by direct measurement of the number and surface area of emulsified droplets using the free ImageJ Image processing and analysis Java software (www.imagej.com). The measurements were used to determine the primary end point of the study: the extent of emulsification of the silicone oil. Several B-scans were recorded from the eye, with the probe vertically oriented on the temporal sclera (the patient looking away from the ultrasound probe). An image was selected that contained the whole vitreous cavity, showing no ultrasound reverberations due to poor contact between the probe and the eye ball.

First, the images were converted to an 8-bit image type. The threshold was set as black and white with a dark background. This enabled background noise to be minimized. On the image, a polygon was drawn over the vitreous cavity, within which the measure-

ment was performed. Within the option to analyze, the measure function was selected and, subsequently, all particles with a size between 25 and 1,000 pixels were automatically counted. The density of the oil particles was determined as the number of particles divided by the area measured. A similar measurement was performed on nonvitrectomized eyes and eyes that had undergone vitrectomy without silicone oil. From these measurements, it was found that inclusion of a particle size between 25 and 1,000 pixels yielded no false-positive (measurement of noise) measurement (Figure 1).

1. Evaluation of extracted silicone oil by direct measurement of emulsified droplets under light microscope view to determine the amount of emulsification formed in the silicone oil during the tamponade, conducted by a masked observer.

Statistical Analysis Framework

Statistical analysis and reporting was performed using the commercially available statistical software SAS system under Windows, version 9.2. For all statistical tests performed, a $P < 0.05$ was used to

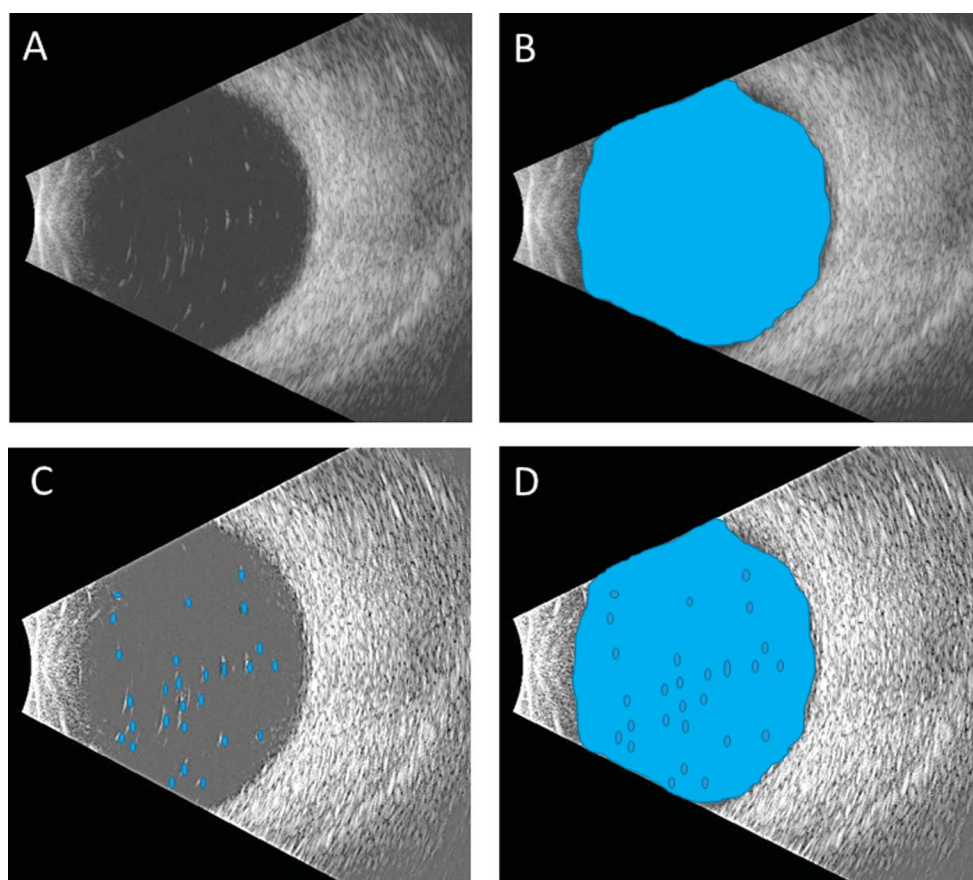


Fig. 1. Measurement of oil emulsification using B-scan ultrasound. **A.** A B-scan is selected showing the largest vitreous cavity (sagittal section). **B.** The area where the oil droplets need to be counted is manually selected by drawing a polygon on the B-scan corresponding to the vitreous cavity. **C.** The computer algorithm automatically detects and counts the oil droplets. **D.** The number of oil droplets is recorded and divided by the area measured (number of pixels) to measure the density of the emulsification.

indicate statistical significance. Because of the absence of a formal sample size calculation, the interpretation of values of *P* was deemed explorative, rather than confirmative. For quantitative parameters, frequency counts and percentages of each category were calculated per treatment group, assessed by descriptive statistics of mean, standard deviation, median, range of the first and third quartiles, and range of minimum and maximum number of valid observations for each treatment group. For qualitative parameters, differences between the two treatment groups were evaluated using a Student's *t*-test for normally distributed variables or a Mann–Whitney *U* test for skewed distributed variables. Overall differences were evaluated using Fisher's exact test (dichotomous response) or chi-square test (exact when indicated). For post-oil removal efficacy data, in which 50% of the patients were also treated with F4H5, comparisons were made with the 4 treatment groups. For quantitative variables, differences were evaluated using analysis of variance of a Kruskal–Wallis test. For qualitative parameters, overall differences were evaluated using a chi-square test (exact when indicated). Statistical analysis was carried out by the Trial Coordination Center, Department of Epidemiology, University Medical Center Groningen, Groningen, the Netherlands.

Compliance

The study was conducted in compliance with the principles of the ICH-GCP, the European Union Directive on Clinical Trials (2001/20/EC), and all local/regional requirements required to conform with the provisions of the Declaration of Helsinki (World Medical Association, Edinburgh, Scotland, 2000). In conformance with Directive 2001/20/EC, a favorable

opinion was issued by the Ethics Committee of the UZ Leuven before the study commenced.

Results

All patients were enrolled in the UZ Leuven Hospital between December 3, 2010, and May 11, 2012. The total study period for each patient extended over 21 months, including 18 months inclusion time, with 3 months of follow-up time. The average age was 68.2 ± 7.5 years, male to female ratio was 22.2% versus 78.8%. On the first day after vitrectomy with silicone oil injection, a 94.3% closure rate was found, whereas 100% closure was recorded before oil removal. No late reopenings after silicone oil removal were observed.

Adverse Events

Serious adverse events. From vitrectomy up to oil removal, the per patient occurrence of serious adverse events was 0% in patients treated with Siluron2000 compared with 5.6% (*N* = 2) in patients treated with Siluron5000 (*P* = 0.49). After oil removal, the occurrence of serious adverse events was 2.8% (*N* = 1) in patients treated with Siluron2000 compared with 0% in patients treated with Siluron5000 (*P* = 1.00). When comparing patients treated with F4H5 versus no use of F4H5, the occurrence of serious adverse events was 0% in patients treated with F4H5 compared with 2.8% (*N* = 1) in patients treated without F4H5 (*P* = 1.00) (Table 1).

Ophthalmic adverse events in study eye. From vitrectomy up to oil removal, the occurrence of ophthalmic adverse events (AEs) was 44% (*N* = 16)

Table 1. Adverse Events

	PPV Oil Injection	6 Weeks After Oil Injection	PPV Oil Removal	6 Weeks After Oil Removal
Occurrence of any ophthalmologic event*				
History		X	X	X
Slit-lamp		X	X	X
Ophthalmoscopy		X	X	X
Occurrence of any AE		X	X	X
Occurrence of PVR on OCT		X	X	X
Change in visual acuity from baseline		X	X	X
Change in Goldmann visual field status from baseline		X		X
Change from baseline in contract sensitivity		X		X
Surgical complication†	X		X	

*Including elevated intraocular pressure, endothelial deposits, oil droplets in anterior chamber, retinal hemorrhage, branch retinal vein occlusion, conjunctivitis, allergic reaction, dry eye, blepharitis, and corneal edema/epitheliopathy.

†Including iris prolapse, iatrogenic retinal break, and wound leakage.

OCT, Optical coherence tomography; PPV, pars plana vitrectomy; PVR, proliferative vitreoretinopathy.

in patients treated with Siluron2000 compared with 42% (N = 15) in patients treated with Siluron5000 ($P = 1.00$). The maximum number of ophthalmic AEs observed was two and three in Siluron2000 and Siluron5000, respectively. After oil removal, the occurrence of ophthalmic AEs was 25% (N = 9) in patients treated with Siluron2000 compared with 28% (N = 10) in patients treated with Siluron5000 ($P = 1.00$). The maximum number of ophthalmic AEs observed was two in both Siluron2000 and Siluron5000. When comparing patients treated with F4H5 versus no use of F4H5, the occurrence of ophthalmic AEs was 22% (N = 8) in patients treated with F4H5 compared with 31% (N = 11) in patients treated without F4H5 ($P = 0.59$). The maximum number of ophthalmic AEs observed was two in both with and without F4H5.

Any adverse events. Before oil removal, the occurrence of AEs was 50% (N = 18) in patients treated with Siluron2000 compared with 56% (N = 20) in patients treated with Siluron5000 ($P = 0.81$). The maximum number of AEs observed was three and four in Siluron2000 and Siluron5000, respectively. After oil removal, the occurrence of AEs was 36% (N = 11) in patients treated with Siluron2000 compared with 31% (N = 11) in patients treated with Siluron5000 ($P = 0.80$). The maximum number of AEs observed was two in both Siluron2000 and Siluron5000.

When comparing patients treated with F4H5 versus no use of F4H5, the occurrence of AEs was 28% (N = 10) in patients treated with F4H5 compared with 39% (N = 14) in patients treated without F4H5 ($P = 0.45$). The maximum number of AEs observed was two in both with and without F4H5.

Perioperative complications. Perioperative complications at vitrectomy were observed in 11% (N = 4) in patients treated with Siluron2000 compared with 0% in patients treated with Siluron5000 ($P = 0.11$). At oil removal, no perioperative complications were observed.

Change in visual function. At Week 6 after vitrectomy, the median improvement from baseline in visual acuity was 10 letters versus 15 letters in patients treated with Siluron2000 and Siluron5000 ($P = 0.51$), respectively. At Week 6 after oil removal, the median improvement from baseline in visual acuity was 14 letters versus 10 letters in patients treated with Siluron2000 and Siluron5000 ($P = 0.11$), respectively. When evaluating the use of F4H5, the median change from baseline in visual acuity was 13 letters versus 11 letters of improvement in patients treated with F4H5 and without F4H5 ($P = 0.76$), respectively.

Change in Goldmann visual field test. At Week 6 after vitrectomy, a borderline significant difference in

the change in the overall evaluation of the Goldmann visual field was observed ($P = 0.056$), mainly because of a difference in visual field test changing from normal to abnormal (19% vs. 46% in Siluron2000 vs. Siluron5000). At Week 6 after oil removal, this difference between Siluron2000 and Siluron5000 was no longer present ($P = 0.70$). When evaluating F4H5 at Week 6 after oil removal, changes in overall evaluation of the Goldmann visual field, with no statistically significant differences in patients treated with F4H5 versus without F4H5, were observed ($P = 0.24$).

Change in color contrast sensitivity test. At Week 6 after vitrectomy, the median change from baseline in the threshold tritan axis (%) was -4.6 (range -47.5 to 62.1) in patients treated with Siluron2000 versus -5.2 (range -71.7 to 36.8) in patients treated with Siluron5000 ($P = 0.30$). At Week 6 after oil removal, the median change from baseline in the threshold tritan axis (%) was -6.8 (range -55.8 to 48.8) in patients treated with Siluron2000 versus -3.0 (range -67.2 to 72.6) in patients treated with Siluron5000 ($P = 0.87$). When evaluating F4H5 at Week 6 after oil removal, changes from baseline in the threshold tritan axis (%) were 0.0 (range -55.8 to 72.6) in patients treated with F4H5 versus -8.0 (range -67.2 to 54.6) in patients treated with Siluron5000 ($P = 0.08$).

Change from baseline in intraocular pressure (glaucoma). At all visits, intraocular pressure was measured. At none of these time points, a significant difference between the study arms could be found in intraocular pressure.

Presence of proliferation on ocular coherence tomography. During the study, proliferation was not noted on ocular coherence tomography in any of the patients.

Efficacy results. Silicone oil handling during surgery. During vitrectomy, with a median time of 1.46 minutes (range 1.17–2.62) to inject, Siluron2000 took statistically significantly less time than Siluron5000, which took 4.13 minutes to inject (range 3.17–4.83, $P < 0.001$). With a median time of 2.78 minutes (range 2.25–4.65), Siluron2000 took statistically significantly less time to remove than Siluron5000, which took 6.83 minutes to remove (range 5.08–9.13, $P < 0.001$) (Figure 2).

Emulsification measurement. Direct emulsification in the removed silicone oil. In 64 patients, data on emulsification was available. Median number of droplets in patients treated with Siluron2000 was 6,640 (range 840–34,480), as compared with 9,220 (range 1,160–38,520) in patients treated with Siluron5000, not statistically significantly different ($P = 0.12$) (Figure 3).

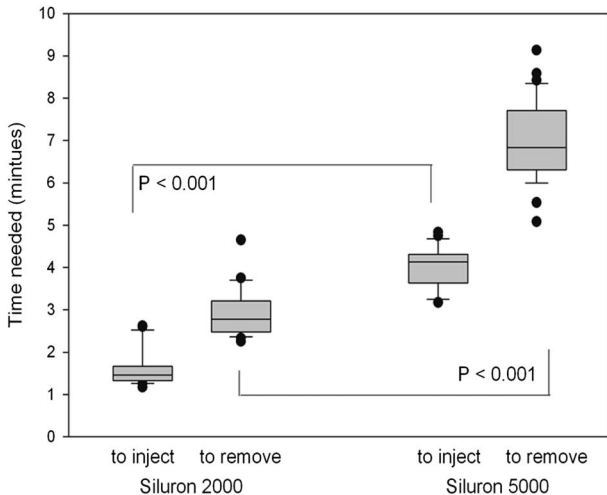


Fig. 2. Time to inject/remove silicone oil. Both injection and removal of Siluron2000 oil through a 23-gauge canula system were significantly faster compared with injection and removal of Siluron5000 oil.

Amount of emulsification assessed by gonioscopy. At 3 months after vitrectomy, gonioscopy was performed in 62 patients. The number of emulsification droplets in patients treated with Siluron2000 did not differ from patients treated with Siluron5000 ($P = 0.54$). At 6 weeks after oil removal, gonioscopy was performed in 66 patients. The number of emulsification droplets in patients treated with Siluron2000 did not differ from patients treated with Siluron5000 ($P = 0.94$). When comparing the use of F4H5, patients treated with F4H5 had less emulsification bubbles than those not treated with F4H5, reaching borderline significance ($P = 0.061$, Figure 4).

Amount of emulsification measured by B-Scan ultrasound. At 6 weeks after oil removal, B-scan

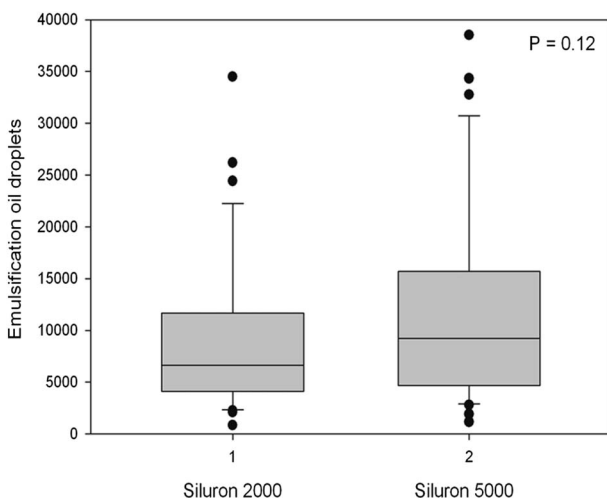


Fig. 3. Amount of emulsification measured. The emulsification measured was similar in both silicone oil types, indicated that Siluron2000 has a similar resistance to emulsification as Siluron5000.

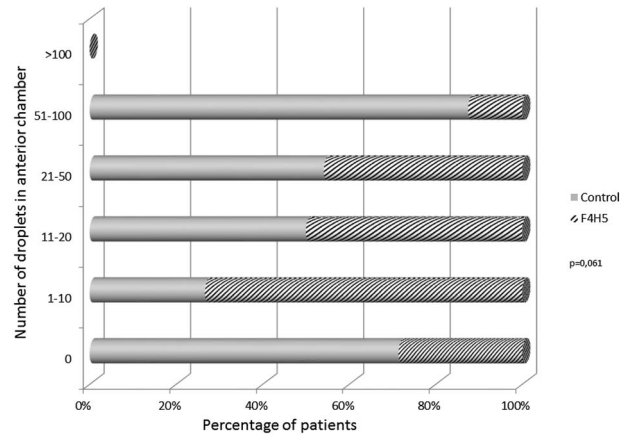


Fig. 4. Amount of emulsification in anterior chamber (gonioscopy). The amount of emulsification was measured by counting the number of oil bubbles in the anterior chamber using gonioscopy. Compared with the control group, there was a trend toward less oil emulsification bubbles found after application of a F4H5 wash.

was performed in all 72 patients. The median number of droplets per 100,000 pixels of measured area in patients treated with Siluron2000 was 12.11 (range 0–122.4), compared with 6.93 (range 0–125.8) in patients treated with Siluron5000, not reaching a statistically significant difference ($P = 0.33$). When comparing the use of F4H5, the median number of droplets per 100,000 pixels of measured area was 8.32 (range 0–125.8) in patients treated with F4H5, not statistically significantly different from the patients not treated with F4H5 (11.05, range 0–96.7; $P = 0.52$).

Discussion

There is an increasing trend in the use of smaller-gauge instrumentation for vitreoretinal procedures. There is also a perceived need for silicone oils to be more “user-friendly”—easier to inject and remove. In the past, choosing to use which silicone oil was simple but limited. Silicone oils of around 1,000 cSt are certainly easier to handle than those around 5,000 cSt, but the lower-viscosity silicone oils are widely perceived to be more prone to emulsification, although this perception is largely more theoretically based than clinically proven. Certainly, *in vitro* studies have shown that silicone oils with higher viscosities are more resistant to emulsification.^{22,32} However, in practice, there has never been a randomized clinical trial to demonstrate that 5,000 cSt oils are more stable inside patients’ eyes. Currently, there is only anecdotal evidence that 5,000 cSt oils are more resistant to emulsification.

There are two main reasons why randomized clinical trials comparing silicone oils have not been

carried out until now. First, it was always considered that there are too many confounding patient-factors to control. It is known that emulsification of silicone oil is dependent on the presence of surfactants to stabilize any droplets that are formed inside the eye. Any breakdown of the blood–ocular barrier would mean that different amounts of large molecules such as protein and glycoprotein might be present. Silicone oils are often used to repair retinal detachment, a condition regularly complicated by release of retinal pigment epithelial cells, glial and inflammatory cells into the vitreous cavity. Even cell membrane material or cell-related molecules, such as retinol, could act as surfactants that promote emulsification. Second, there has been no objective method available for quantifying emulsification.

In recent years, the practice of adding high–molecular weight components (423 kD) to standard silicone oil (as a 5% or 10% solution) was described.²³ The addition of these high–molecular weights not only increases shear viscosity, but also the extensional viscosity, such that the new oil mixture is more resistant to emulsification. Simultaneously, it was shown in vitro that these silicone oil solutions are easier to inject and to remove.³⁵ The 2 products (with a 5% and 10% additive) have a kinematic viscosity of 2,000 cSt and 5,000 cSt and are commercially known as Siluron2000 and SiluronXtra. There are, until now, no clinical trials providing an evidence base to justify their use.

The study results indicate the following:

- Siluron2000 provided superior handling compared with Siluron5000, because both injection and removal of the Siluron2000 were significantly faster than those for Siluron5000 (Figure 2).
- The amount of emulsification measured was not more pronounced in patients treated using Siluron2000 compared with that experienced with patients treated using Siluron5000 (Figure 3).

However, the amount of emulsification in the anterior chamber measured through gonioscopy showed a trend toward less emulsification after F4H5 wash, which was borderline significant regarding the small sample size of the trial (Figure 4).

This study was designed to overcome two of the major problems preventing randomized clinical trials. First, patients with FTMH were chosen. Outside UZ Leuven, the routine use of silicone oil in the treatment of FTMH is unusual. Nonetheless, it has been a standard practice at the study center and the excellent results already achieved have been published in previous articles.^{11,12} The advantage of choosing patients with FTMH is clear. None of the patients had inflam-

mation, breakdown of blood ocular barrier, or retinal detachment. They could be regarded as “virgin” eyes and certainly, together, they formed a very uniform group allowing the randomized controlled trial to be carried out.

A variety of end points were evaluated. Most importantly, ultrasound measurement was used to quantify emulsification. No difference in the rate of emulsification between Siluron2000 and Siluron5000 was found. However, these results might not be generalizable for all indications of silicone oil use. First, FTMH patients are probably not high-risk patients for emulsification. Second, it is difficult to know whether there could be a Type 2 statistical error. No previous meaningful quantification of emulsification has been published, making it difficult to perform power calculations. Nonetheless, this study represents the first randomized human clinical trial on two different silicone oils and provides some support to the published in vitro evidence on Siluron2000.

In summary, Siluron2000 silicone oil is equally safe and effective as Siluron5000 oil but allows for better handling with the potential of reducing procedure time. The time required to inject and remove Siluron2000 is similar to that of 1,000 cSt silicone oil. The data showed that the amount of emulsification in the anterior chamber measured through gonioscopy showed a trend toward less emulsification after F4H5 wash (borderline significant). The addition of F4H5 seems to enhance emulsification and reduce post-operative complications.

Key words: emulsification, full-thickness macular hole, silicone oil, Siluron2000, Siluron5000, F4H5, vitreous washout.

Acknowledgments

The authors thank Inge Vriens, study nurse, for practical support in the study; Trial Coordination Center (TCC), Department of Epidemiology, University Medical Center, Groningen, the Netherlands, for the data monitoring and data analysis; and Sara Sharpe (www.thecreativepractice.com) for support in preparation of the article.

References

1. Cibis PA, Becker B, Okun E, Cnaan S. The use of liquid silicone in retinal detachment surgery. *Arch Ophthalmol* 1962;68:590–599.
2. Zivojnović R, Mertens DA, Peperkamp E. Liquid silicone in amotio surgery (II). Report on 280 cases—further development of the technic [In German]. *Klin Monbl Augenheilkd* 1982; 181:444–452.

3. Altan T, Acar N, Kapran Z, et al. Transconjunctival 25-gauge sutureless vitrectomy and silicone oil injection in diabetic tractional retinal detachment. *Retina* 2008;28:1201–1206.
4. Castellarin A, Grigorian R, Bhagat N, et al. Vitrectomy with silicone oil infusion in severe diabetic retinopathy. *Br J Ophthalmol* 2003;87:318–321.
5. Shunmugam M, Ang GS, Lois N. Giant retinal tears. *Surv Ophthalmol* 2014;59:192–216.
6. Kapur R, Birnbaum AD, Goldstein DA, et al. Treating uveitis-associated hypotony with pars plana vitrectomy and silicone oil injection. *Retina* 2010;30:140–145.
7. Ghosh YK, Banerjee S, Konstantinidis A, et al. Surgical management of optic disc pit associated maculopathy. *Eur J Ophthalmol* 2008;18:142–146.
8. Papadopoulou DN, Petropoulos IK, Mangioris G, et al. Pars plana vitrectomy in the treatment of severe complicated toxoplasmic retinochoroiditis. *Eur J Ophthalmol* 2011;21:83–88.
9. Azen SP, Scott IU, Flynn HW, et al. Silicone oil in the repair of complex retinal detachments. A prospective observational multicenter study. *Ophthalmology* 1998;105:1587–1597.
10. Sabti KA, Raizada S. Endoscope-assisted pars plana vitrectomy in severe ocular trauma. *Br J Ophthalmol* 2012;96:1399–1403.
11. Van De Moere A, Stalmans P. Anatomical and visual outcome of macular hole surgery with infracyanine green-assisted peeling of the internal limiting membrane, endodrainage, and silicone oil tamponade. *Am J Ophthalmol* 2003;136:879–887.
12. Schurmans A, Van Calster J, Stalmans P. Macular hole surgery with Inner limiting membrane peeling, endodrainage, and heavy silicone oil tamponade. *Am J Ophthalmol* 2009;147:495–500.
13. Riedel KG, Gabel VP, Neubauer L, et al. Intravitreal silicone oil injection: complications and treatment of 415 consecutive patients. *Graefes Arch Clin Exp Ophthalmol* 1990;228:19–23.
14. Trigui A, Gharbi J, Hamdi S, et al. Long-term use of silicone oil: indications and tolerance [In French]. *J Fr Ophtalmol* 2013;36:117–123.
15. Light DJ. Silicone oil emulsification in the anterior chamber after vitreoretinal surgery. *Optometry* 2006;77:446–449.
16. Ichhpujani P, Jindal A, Jay Katz L. Silicone oil induced glaucoma: a review. *Graefes Arch Clin Exp Ophthalmol* 2009;247:1585–1593.
17. Matić S, Suić SP, Biuk D, et al. Influence of silicone oil tamponade after vitrectomy on intraocular pressure. *Coll Antropol* 2013;37:227–235.
18. Kociok N, Gavranic C, Kirchhof B, Joussem AM. Influence on membrane-mediated cell activation by vesicles of silicone oil or perfluorohexyloctane. *Graefes Arch Clin Exp Ophthalmol* 2005;243:345–358.
19. La Heij EC, Hendrikse F, Kessels AG. Results and complications of temporary silicone oil tamponade in patients with complicated retinal detachments. *Retina* 2001;21:107–114.
20. Heidenkummer HP, Messmer EM, Kampik A. Recurrent vitreoretinal membranes in intravitreal silicon oil tamponade. Morphologic and immunohistochemical studies. *Ophthalmologie* 1996;93:121–125.
21. Crisp A, de Juan E, Tiedeman J. Effect of silicone oil viscosity on emulsification. *Arch Ophthalmol* 1987;105:546–550.
22. Heidenkummer HP, Kampik A, Thierfelder S. Emulsification of silicone oils with specific physicochemical characteristics. *Graefes Arch Clin Exp Ophthalmol* 1991;229:88–94.
23. Williams RL, Day M, Garvey MJ, et al. Increasing the extensional viscosity of silicone oil reduces the tendency for emulsification. *Retina* 2010;30:300–304.
24. Caramoy A, Schröder S, Fauser S, Kirchhof B. In vitro emulsification assessment of new silicone oils. *Br J Ophthalmol* 2010;94:509–512.
25. Nakamura K, Refojo MF, Crabtree DV, Leong FL. Analysis and fractionation of silicone and fluorosilicone oils for intraocular use. *Invest Ophthalmol Vis Sci* 1990;31:2059–2069.
26. Schwert GW. *Outlines of biochemistry*. R. A. GORTNER, 3rd edition edited by R. A. Gortner, Jr., and W. A. Gortner, Wiley, New York, 1949, 1078 pp., \$7.00. *J Polym Sci* 1950;5:637–637.
27. Bartov E, Pennarola F, Savion N, et al. A quantitative in vitro model for silicone oil emulsification. Role of blood constituents. *Retina* 1992;12:S23–S27.
28. Savion N, Alhalel A, Treister G, Bartov E. Role of blood components in ocular silicone oil emulsification. Studies on an in vitro model. *Invest Ophthalmol Vis Sci* 1996;37:2694–2699.
29. Chan YK, Ng CO, Knox PC, et al. Emulsification of silicone oil and eye movements. *Invest Ophthalmol Vis Sci* 2011;52:9721–9727.
30. Nakamura K, Refojo MF, Crabtree DV. Factors contributing to the emulsification of intraocular silicone and fluorosilicone oils. *Invest Ophthalmol Vis Sci* 1990;31:647–656.
31. De Silva DJ, Lim KS, Schulenburg WE. An experimental study on the effect of encircling band procedure on silicone oil emulsification. *Br J Ophthalmol* 2005;89:1348–1350.
32. Heidenkummer HP, Kampik A, Thierfelder S. Experimental evaluation of in vitro stability of purified polydimethylsiloxanes (silicone oil) in viscosity ranges from 1000 to 5000 centistokes. *Retina* 1992;12:S28–S32.
33. Francis JH, Latkany PA, Rosenthal JL. Mechanical energy from intraocular instruments cause emulsification of silicone oil. *Br J Ophthalmol* 2007;91:818–821.
34. Dresch JH, Menz DH. Preparation and processing of vitreoretinal instrumentation and equipment as a risk factor for silicone oil emulsification. *Retina* 2004;24:110–115.
35. Rizzo S, Romagnoli MC, Genovesi-Ebert F, Belting C. Surgical results of heavy silicone oil HWS-45 3000 as internal tamponade for inferior retinal detachment with PVR: a pilot study. *Graefes Arch Clin Exp Ophthalmol* 2011;249:361–367.
36. Williams RL, Day MJ, Garvey MJ, et al. Injectability of silicone oil-based tamponade agents. *Br J Ophthalmol* 2011;95:273–276.
37. Stappler T, Morphis G, Irigoyen C, Heimann H. Is there a role for long-term silicone oil tamponade for more than twelve months in vitreoretinal surgery? *Ophthalmologica* 2011;226:36–41.
38. Maier MM, Engelmann V, Pfrommer S, et al. Early emulsification of silicone oil (2000 cs) in minimally invasive transconjunctival vitreoretinal surgery. *Klinische Monatsheilkunde* 2011;228:477–479.
39. Pastor JC, Zarco JM, Del Nozal MJ, et al. Clinical consequences of the use of highly purified silicone oil. Comparative study of highly and less purified silicone oil. *Eur J Ophthalmol* 1998;8:179–183.
40. Liang Y, Kociok N, Leszczuk M, et al. A cleaning solution for silicone intraocular lenses: “sticky silicone oil”. *Br J Ophthalmol* 2008;92:1522–1527.
41. Stappler T, Williams R, Wong D. F4H5: a novel substance for the removal of silicone oil from intraocular lenses. *Br J Ophthalmol* 2010;94:364–367.