Heavier-than-Water Silicone Oil Mixture as a Long-Term Tamponade Agent: A Pilot Study

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Key Words

Densiron • F₆H₈ • Proliferative vitreoretinopathy •
Perfluorohexyloctane • Silicone oil • Retinal detachment •
Tamponade

Abstract

Purpose: To evaluate the tamponade effect on the retina of a heavier-than-water silicone oil mixture and to compare it with the effect of silicone oil. **Methods:** Prospective, non-randomised, comparative pilot study. Phakic/pseudophakic patients with retinal detachment undergoing vitrectomy with Densiron 68 or silicone oil were recruited. The 'separation volume', defined as the relative volume of the space between intraocular tamponade agent and retina, was estimated using magnetic resonance imaging in both groups and compared. **Results:** Nine participants were included; 4 received silicone oil and 5 Densiron 68. The mean separation volume was statistically significantly larger in the silicone oil group ($0.477 \pm 0.419 \text{ cm}^3$) than in the Densiron group ($0.042 \pm 0.013 \text{ cm}^3$; $p = 0.014$). **Conclusions:** In this study Densiron achieved an excellent tamponade effect in the retina.

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Introduction

Vitreoretinal diseases, including retinal detachment (RD), remain a leading cause of treatable blindness [1]. Recent improvements in surgical techniques and intraocular short- and long-term tamponade agents have increased the success rates of vitreoretinal surgery [2], in which vitreous substitutes play a major role. Previously, hyaluronic acid, gas, silicone oil, perfluorocarbons, semifluorinated alkanes and fluorosilicone have been used as long-term endotamponade agents with variable results [3].

Cibis et al. [4] first described the use of silicone oil in retinal surgery. Despite initial concerns about potentially toxic effects of silicone oil on the retina [5, 6], silicone oil has become one of the preferred intraocular tamponade agents to be used in the treatment of RD complicated by proliferative vitreoretinopathy (PVR). Several studies have demonstrated its safety and efficacy in the management of complicated RD [7–10]. Due to its low specific gravity (0.97), however, one of the major limitations of silicone oil is its apparent inability to tamponade the inferior retina [11], where PVR has a tendency to occur [12].

Perfluorocarbons, semifluorinated alkanes and fluorosilicone have a specific gravity higher than that of water (1.7–2.0, 1.35 and 1.35, respectively) and, thus, are expect-

ed to be better tamponade agents for the inferior retina. Perfluorocarbons, however, do not appear to be tolerated well when left in the eye for extended periods of time [13–17]. Similarly, it is not clear whether fluorosilicones and semifluorinated alkanes are better tolerated, and both have been shown to incite an inflammatory response in the eye [18–21]. Furthermore, semifluorinated alkanes (perfluorohexyloctane, F_6H_8) used alone have a tendency to emulsify early, with a subsequent reduction in the extent of retina covered by the agent [22].

Recently, a mixture of perfluorohexyloctane (F_6H_8) and 5,000-mPa·s silicone oil (Densiron 68; Fluoron Co., Neu-Ulm, Germany) has become available. Densiron has a specific gravity of 1.06 g/cm³ and a viscosity of 1,387 mPa·s and has now received an EU certification (EU No. 0535). A mixture of F_6H_8 with silicone oil, with a specific gravity of 1.06 g/cm³, was shown to provide a better inferior tamponade effect on the retina in a model eye chamber [23]. Furthermore, Wong et al. [24] recently published the results of a non-comparative pilot study using Densiron 68 in a group of 42 patients with RD complicated by PVR, RD arising from posterior or inferior retinal breaks, and patients with RD who were unable to posture. The anatomical success rate after a single surgery using Densiron was 81%, which improved to 93% with further surgery. A statistically significant improvement in visual acuity was also observed [from 1.41 (SD: 0.64) preoperatively to 0.94 (SD: 0.57) postoperatively; $p = 0.001$]. In their selected cohort of patients, there was no evidence of dispersion or excessive inflammation related to the use of Densiron 68. Densiron 68 was selected as a tamponade agent in a multicentre, randomised clinical trial comparing the efficacy of this heavier-than-water tamponade agent with that of silicone oil [25].

Based on its characteristics, it could be expected that Densiron 68 provides a good tamponade effect to both the superior and inferior retina; there are scarce objective data available, however, to support this. The purpose of the current pilot study was to evaluate objectively, using magnetic resonance imaging (MRI), the efficacy of Densiron 68 as a tamponade agent, specifically with regard to its effect on covering the inferior retina.

Patients and Methods

This was a prospective, non-randomised, comparative, clinical pilot study. Nine consecutive patients undergoing pars plana vitrectomy and long-term internal tamponade (3 months) with conventional silicone oil (5,000 cSt) or Densiron 68 were eligible to participate in this study in the period between June 2008 and

September 2009. All patients had rhegmatogenous RD, 6 of them had previously failed surgery or surgeries. All but 2 cases had PVR grades of $\geq C$. Visual acuity including distance and reading vision as well as anterior and posterior segment examination using slit-lamp biomicroscopy and indirect ophthalmoscopy were performed at each follow-up visit. Any inflammatory response clinically observed (cells in the anterior chamber or vitreous cavity) and evidence of emulsification of the tamponade agent (dispersion of the tamponade into small droplets) during the follow-up period was recorded.

All patients underwent MRI to determine the degree of posterior segment filling obtained postoperatively with each of the endotamponade agents used (silicone oil and Densiron 68). MRI was performed in all cases between 1 and 2 weeks postoperatively. T_1 -weighted images acquired by the fat suppression technique were used. In order to achieve the best visualisation of the eye and its structures, a surface coil was used when acquiring the images [26, 27]. MRI scans were obtained with the patients lying flat on their back. The space between the tamponade agent and the retina (volume of separation of the tamponade agent from the ocular wall) was assessed by MRI readers in a masked fashion based on axial and coronal T_1 -weighted images. The space free of tamponade agent was seen as an area with an intermediate signal and with a crescent shape in both axial and coronal planes at the equator.

The following observations were made on each plane:

- The image with the crescent having the longest diameter was identified in the axial plane (reference image). The distance between the outer edges of the crescent (a) and the maximum thickness ($t1$) of the crescent were measured in centimetres (fig. 1a, left).
- Similar measurements were obtained from images immediately above ($n = 1$) and below ($n = 1$) the reference image.
- The above two steps were repeated for the coronal plane, yielding values b for distance and $t2$ for thickness (fig. 1a, right).
- An average of the 3 values was calculated to yield the average distances A and B and average thickness T.

As it was found that the space between the tamponade agent and the retina was small, its volume was approximated to that of a thin slab with the dimension $A \times B \times T$ (fig. 1b). The final value, expressed in cubic centimetres, describes the relative volume of the space between intraocular tamponade agent and retina, which we will refer to as the 'separation volume' or 'underfill' in this study.

Statistical Analysis of the Data

The Mann-Whitney test was used to compare differences in separation volume between the silicone oil and Densiron groups. $p \leq 0.05$ was considered to be statistically significant. Local ethics approval and written informed consent of the patients were obtained prior to the initiation of the study.

Results

A total of 9 participants, 6 men and 5 women, with a median age of 64 years (interquartile range: 54–76 years) were included in the study (table 1). Four participants received silicone oil, the remaining 5 Densiron 68 (table 1).

Fig. 1. a Sketch demonstrating measurements obtained from axial and coronal MR images. The image with the crescent having the longest diameter was identified in the axial (left) and coronal (right) planes (reference images). The distance between the outer edges of the crescent (*a*, *b*) and the maximum thickness (*t*) of the crescent were measured in centimetres. Similar measurements

were obtained from images immediately above (*n* = 1) and below (*n* = 1) the reference image. **b** An average of the 3 values (for *a*, *b* and *t*) was calculated to yield the average distances *A* and *B* and the average thickness *T*. As the space between tamponade agent and retina was found to be small, its volume was approximated to that of a thin slab with the dimension *A* × *B* × *T*.

Table 1. Preoperative patient characteristics, types of endotamponade used, postoperative outcomes and complications

Patient No.	Eye	Type of RD	Preop VA	Quadrants of RD	PVR-C	Lens status	Oil used	FU months	Postop VA	Retina status	Comp
1	R	RRD*	HM	4	yes	pseudophakic	D	10	6/48	flat	no
2	R	RRD*	CF	3	yes	pseudophakic	D	11	CF	flat	no
3	R	RRD	6/36	3	yes	pseudophakic	D	7	6/36	flat	no
4	R	RRD	HM	3	yes	pseudophakic	S	20	6/60	pocket of SRF anterior to peripheral laser barrier detached ²	no
5	R	RRD*	HM	4	yes	pseudophakic	D	16	HM	failure; oil in AC	failure; oil in AC
6	L	RRD	HM	2	yes	phakic	S	20	6/12	flat	no
7	R	RRD*	3/60	4	no	pseudophakic	D	23	6/48	pocket of SRF anterior to peripheral laser barrier detached ²	no
8	L	RRD*, ¹	CF	4	yes	pseudophakic	S	6	3/60	failure	failure
9	L	RRD*, ¹	HM	2	no	pseudophakic	S	26	HM	failure	failure

R = Right eye; L = left eye; Preop = preoperative; Postop = postoperative; VA = visual acuity; RRD = rhegmatogenous RD; Comp = intraoperative and postoperative complications; RRD* = recurrent RRD; PVR-C = PVR of grade ≥C; D = Densiron; S = silicone oil; FU = duration of follow-up; HM = hand movement; CF = counting fingers; SRF = subretinal fluid; AC = anterior chamber.

¹ Initially ruptured globe that underwent primary repair followed by RD repair with the tamponade agent.

² Retina detached following removal of the tamponade agent (S or D).

The mean separation volume was larger in the silicone oil group ($0.477 \pm 0.419 \text{ cm}^3$) than in the Densiron group ($0.042 \pm 0.013 \text{ cm}^3$); this difference was statistically significant ($p = 0.014$) (fig. 2). No clinically relevant intraocular inflammation was observed in either group. Complications in the silicone and Densiron 68 groups are detailed in table 1. The patients were followed for a mean of

16 months (range: 6–26 months). The retinal tamponade was removed from all eyes at the last follow-up. Surgery failed to reattach the retina in 1 patient of the Densiron 68 group and in 2 of the silicone oil group; in these, the retina detached following removal of the tamponade agent (table 1). Two of the 3 failures underwent further procedures; 1 patient declined further surgery.

Fig. 2. MRI of silicone oil (S)- and Densiron (D)-filled eyes demonstrating the 'separation volume'. Top row: left = patient 1, centre = patient 2, right = patient 3. Centre row: left = patient 4, centre = patient 5, right = patient 6. Bottom row: left = patient 7, centre = patient 8, right = patient 9 (table 1).

Discussion

In our study a more effective tamponade to the superior and inferior retina was observed following the use of Densiron 68 when compared with silicone oil. To our knowledge, this is the first published study in which an objective evaluation and comparison of the tamponade effects of these two agents was undertaken using MRI. Although, based on current findings, a nearly full filling of the vitreous cavity can be achieved with either silicone oil or Densiron 68, it appears that this is more frequently obtained using the latter tamponade agent (fig. 2). Furthermore, it appeared that Densiron 68 equally covered the superior and inferior retina. It could, accordingly, be used for any RD and, based on the results of this small pilot study, it may be superior to silicone oil in the treatment of inferior RD complicated by PVR. It has been speculated that, due to gravity, PVR-associated growth factors concentrate in the inferior retina [28]. Silicone oil, being lighter than water and – as shown in this study – less frequently able than Densiron 68 to appose itself to the inferior retina, would allow the existence of a space

between its own meniscus and the inferior retina, where PVR-associated growth factors could accumulate [28]. In contrast, Densiron 68 would prevent the above events to take place by eliminating this inferior space.

Another possible advantage of using Densiron 68 in treating inferior RD would be that patients would not need to posture postoperatively. The complete filling observed in the current study with Densiron 68 may explain the good anatomical outcomes reported of patients with full-thickness macular holes, including those that failed to close following an initial surgery, without the need of postoperative posturing [29–31]. Moreover, the full fill of the vitreous cavity achieved with Densiron 68 would make barrier laser application easier prior to oil removal; such a manoeuvre was shown to reduce the rate of retinal redetachment following silicone oil removal [32].

In the current study, complications observed included failure in 3 cases (2 in the silicone oil group and 1 in the Densiron group) and passage of silicone oil from the Densiron 68 silicone oil- F_6H_8 mixture into the anterior chamber in 1 patient in the Densiron group. Although having a good tamponade effect is essential to achieve break closure, it is not sufficient to prevent retinal redetachment. The latter depends on several other factors, including 'missing tears' intraoperatively and continuous traction postoperatively. Thus, although a good tamponade may help the vitreoretinal surgeon to increase their anatomical surgical success, it is not a guarantee of achieving retinal reattachment.

Long-term complications of silicone oil seem to be well established; this may not be the case for Densiron 68. To date, it appears that common complications associated with the use of Densiron 68 are posterior capsular opacification, intraocular inflammation, dispersion of this tamponade agent and increased intraocular pressure [33]. Dispersion is well known to happen also when conventional silicone oil is used [34]. The complication spectrum of Densiron 68 seems to be similar to that of other oil tamponades [35]. Wong et al. [36] compared the postoperative intraocular pressure in patients treated with Densiron and conventional silicone oil and found higher intraocular pressure in the Densiron group in the early postoperative period (2 weeks); however, the difference was not statistically significant at later stages. Mackiewicz et al. [37] studied 'in vivo' the retinal tolerance to heavy silicone oil including Densiron and conventional silicone oils in rabbits. They found that all tamponades studied (silicone oils, Densiron and Oxane HD) were well tolerated for 3 months based on

histopathology and electroretinographic findings. In addition, intraocular inflammation and cataract formation seemed to be comparable in all groups.

The current study has several limitations including: the small number of cases enrolled; the fact that all MR images were obtained with the patient supine, which may have made it more difficult to determine the presence of a separation volume superiorly in the cases filled with Densiron, and the fact that the images were obtained only once during the course of the follow-up, thus not allowing an evaluation of possible changes in separation volume that may take place as a result of dispersion of the endotamponade agent over time. Nonetheless, the findings suggest that, frequently, Densiron allows obtaining an excellent coverage of the superior and inferior retina and may be considered a good option to treat RD affecting inferior retinae, especially those complicated by PVR.

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Disclosure Statement

The authors have no conflict of interest with regard to any of the material(s) presented.

References

- Sodhi A, Leung LS, Do DV, Gower EW, Schein OD, Handa JT: Recent trends in the management of rhegmatogenous retinal detachment. *Surv Ophthalmol* 2008;53:50–67.
- Johnson Z, Ramsay A, Cottrell D, Mitchell K, Stannard K: Triple cycle audit of primary retinal detachment surgery. *Eye (Lond)* 2002;16:513–518.
- Foster WJ: Vitreous substitutes. *Expert Rev Ophthalmol* 2008;3:211–218.
- Cibis PA, Becker B, Okun E, Canaan S: The use of liquid silicone in retinal detachment surgery. *Arch Ophthalmol* 1962;68:590–599.
- Jalkh AE, McMeel JW, Kozlowski IM, Schepens CL: Silicone oil retinopathy. *Arch Ophthalmol* 1986;104:178–179.
- Mukai N, Lee PF, Oguri M, Schepens CL: A long-term evaluation of silicone retinopathy in monkeys. *Can J Ophthalmol* 1975;10:391–402.
- Abrams GW, Azen SP, McCuen BW 2nd, Flynn HW Jr, Lai MY, Ryan SJ: Vitrectomy with silicone oil or long-acting gas in eyes with severe proliferative vitreoretinopathy: results of additional and long-term follow-up. *Silicone Study Report 11. Arch Ophthalmol* 1997;115:335–344.
- McCuen BW 2nd, Azen SP, Stern W, Lai MY, Lean JS, Linton KL, Ryan SJ: Vitrectomy with silicone oil or perfluoropropane gas in eyes with severe proliferative vitreoretinopathy. *Silicone Study Report 3. Retina* 1993;13:279–284.
- Vitrectomy with silicone oil or perfluoropropane gas in eyes with severe proliferative vitreoretinopathy: results of a randomized clinical trial. *Silicone Study Report 2. Arch Ophthalmol* 1992;110:780–792.
- Vitrectomy with silicone oil or sulfur hexafluoride gas in eyes with severe proliferative vitreoretinopathy: results of a randomized clinical trial. *Silicone Study Report 1. Arch Ophthalmol* 1992;110:770–779.
- Wong D, Lois N: Perfluorocarbons and semifluorinated alkanes. *Semin Ophthalmol* 2000;15:25–35.
- Singh AK, Glaser BM, Lemor M, Michels RG: Gravity-dependent distribution of retinal pigment epithelial cells dispersed into the vitreous cavity. *Retina* 1986;6:77–80.
- Devin F, Jourdan T, Saracco JB, Lucciani A: Experimental tolerance to perfluorodecalin used in prolonged intraocular tamponade. *Ophthalmologica* 1995;209:306–314.
- Chang S, Sparrow JR, Iwamoto T, Gershbein A, Ross R, Ortiz R: Experimental studies of tolerance to intravitreal perfluoro-*n*-octane liquid. *Retina* 1991;11:367–374.
- Stolba U, Krepler K, Velikay M, Binder S: Anterior segment changes in rabbits after experimental aqueous replacement with various amounts of different perfluorocarbon liquids. *Graefes Arch Clin Exp Ophthalmol* 1999;237:501–507.
- Velikay M, Stolba U, Wedrich A, Li Y, Datlinger P, Binder S: The effect of chemical stability and purification of perfluorocarbon liquids in experimental extended-term vitreous substitution. *Graefes Arch Clin Exp Ophthalmol* 1995;233:26–30.
- Moreira H, de Queiroz JM Jr, Liggett PE, McDonnell PJ: Corneal toxicity study of two perfluorocarbon liquids in rabbit eyes. *Cornea* 1992;11:376–379.
- Pastor JC, Lopez MI, Saornil MA, Refojo MF: Intravitreal silicone and fluorosilicone oils: pathologic findings in rabbit eyes. *Acta Ophthalmol* 1992;70:651–658.
- Eckardt C, Schmidt D, Czank M: Intraocular tolerance to silicone oils of different specific gravities: an experimental study. *Ophthalmologica* 1990;201:133–139.
- Vote B, Wheen L, Clurue A, Teoh H, McGeorge A: Further evidence for proinflammatory nature of perfluorohexyloctane in the eye. *Clin Experiment Ophthalmol* 2003;31:408–414.
- Hiscott P, Magee RM, Colthurst M, Lois N, Wong D: Clinicopathological correlation of epiretinal membranes and posterior lens opacification following perfluorohexyloctane tamponade. *Br J Ophthalmol* 2001;85:179–183.
- Kirchhof B, Wong D, van Meurs J, Hilgers RD, Macek M, Lois N, Schrage NF: Use of perfluorohexyloctane as a long-term internal tamponade agent in complicated retinal detachment surgery. *Am J Ophthalmol* 2002;133:95–101.
- Wetterqvist C, Wong D, Williams R, Stappeler T, Herbert E, Freeburn S: Tamponade efficiency of perfluorohexyloctane and silicone oil solutions in a model eye chamber. *Br J Ophthalmol* 2004;88:692–696.
- Wong D, van Meurs JC, Stappeler T, Groenewald C, Pearce IA, McGalliard JN, Manousakis E, Herbert EN: A pilot study on the use of a perfluorohexyloctane/silicone oil solution as a heavier than water internal tamponade agent. *Br J Ophthalmol* 2005;89:662–665.

- 25 Comparison High-Density Silicone Oils in Retinal Detachment. NCT00403702. <http://clinicaltrials.gov/ct2/show/NCT00403702>.
- 26 Herrick RC, Hayman LA, Maturi RK, Diaz-Marchan PJ, Tang RA, Lambert HM: Optimal imaging protocol after intraocular silicone oil tamponade. *AJNR Am J Neuroradiol* 1998;19:101–108.
- 27 de Potter P, Shields JA, Shields CL: *MRI of the Eye and Orbit*. Philadelphia, Lippincott Williams & Wilkins, 1995.
- 28 Jousseaume AM, Kirchhof B, Schrage N, Ocklenburg C, Hilgers RD: Heavy silicone oil versus standard silicone oil as vitreous tamponade in inferior PVR (HSO Study): design issues and implications. *Acta Ophthalmol Scand* 2007;85:623–630.
- 29 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.
- 30 Lappas A, Foerster AM, Kirchhof B: Use of heavy silicone oil (Densiron-68) in the treatment of persistent macular holes. *Acta Ophthalmol* 2009;87:866–870.
- 31 Saeed MU, Heimann H, Wong D, Gibran SK: Heavy silicone oil tamponade after failed macular hole surgery with perfluoropropane (C₃F₈): a report of five cases. *Graefes Arch Clin Exp Ophthalmol* 2009;247:707–709.
- 32 Tufail A, Schwartz SD, Gregor ZJ: Prophylactic argon laser retinopexy prior to removal of silicone oil: a pilot study. *Eye (Lond)* 1997;11:328–330.
- 33 Li W, Zheng J, Zheng Q, Wu R, Wang X, Xu M: Clinical complications of Densiron 68 intraocular tamponade for complicated retinal detachment. *Eye (Lond)* 2010;24:21–28.
- 34 Ciardella AP, Langton K, Chang S: Intraocular dispersion of perfluorocarbon liquids in silicone oil. *Am J Ophthalmol* 2003;136:365–367.
- 35 Heimann H, Stappler T, Wong D: Heavy tamponade. 1. A review of indications, use, and complications. *Eye (Lond)* 2008;22:1342–1359.
- 36 Wong D, Kumar I, Quah SA, Ali H, Vallderas X, Romano MR: Comparison of post-operative intraocular pressure in patients with Densiron-68 vs conventional silicone oil: a case-control study. *Eye (Lond)* 2009;23:190–194.
- 37 Mackiewicz J, Mühling B, Hiebl W, Meinert H, Maaijwee K, Kociok N, Lüke C, Zagorski Z, Kirchhof B, Jousseaume AM: In vivo retinal tolerance of various heavy silicone oils. *Invest Ophthalmol Vis Sci* 2007;48:1873–1883.