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Heavy tamponade 2 Densiron 68® in routine clinical practice: anatomical and functional outcomes of a consecutive case series

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Abstract

Purpose **To evaluate the safety and efficacy of Densiron 68® in the clinical management of complex vitreoretinal cases with inferior retinal pathology.**

Methods **We present a prospective interventional non-comparative case series of 122 eyes of 121 consecutive patients. The primary end point was anatomical re-attachment of the retina, defined as retinal re-attachment in the absence of any tamponade agent. The secondary end point was to record the visual function and surgical complications. Inclusion criteria were proliferative vitreoretinopathy, posterior or inferior retinal breaks, and the patient's inability to posture.**

Results **Patients were 59.9 years (±19.6), (m/f = 72:49), (R/L = 65:57). Seventy-seven (63.1%) had previous unsuccessful retinal surgery and 45 had Densiron 68 at first procedure. The extent of the detachments was 2.21 quadrants (±1.07) with macular involvement in 66 cases (54%). Eighty-seven (71.3%) patients achieved retinal re-attachment with one retinal operation and ultimately no tamponade, 102 (83.6%) achieved retinal re-attachment with more than one operation and ultimately no tamponade, and 112 (91.3%) patients achieved flat retina with tamponade *in situ*. Visual acuity rose from 1.38 LogMar (±0.87) to 1.06 (±0.83) ($P = 0.007$). Densiron was removed after 135 days (±73.2; range 35–405)**

Conclusion **No tamponade agent can provide simultaneous support for the superior as well as the inferior retina; therefore, a tamponade agent that 'sinks' is a welcome new tool at the surgeon's disposal. The sequential use of heavy silicone oil followed by conventional silicone oil may be an acceptable management strategy in recurrent detachment.**

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Introduction

For many decades, silicone oil has been the only acceptable long-term tamponade.[1,2] Prolonged tamponade is used mainly for cases of proliferative vitreoretinopathy (PVR), trauma, and giant retinal tears. In some instances, its use is extended to include cases of complicated retinal detachments (RD) without severe PVR, with multiple failed previous operations, with multiple and awkward distribution of retinal breaks.[3] The availability of heavy silicone oil (HSO) such as Densiron 68® provides us with an alternative for long-term tamponade. PVR has a propensity to occur in the inferior fundus;[4] recurrent RD especially after vitrectomy (with gas or oil) also affect the inferior retina. HSO might represent a welcome new addition to our choice.

Silicone oil bubbles are relatively hydrophobic; they subtend a large contact angle against the retina and therefore they have a rounded profile.[5] In a series of model eye experiments, we demonstrated that their ability to displace aqueous from the surface of the retina is poor as compared to gas such that a slight under-fill with silicone might leave large areas of the retina unsupported.[6] Others have made the same point that for silicone oil to be

effective, it needs to fill the vitreous cavity 100%.[7] A complete fill however, presupposes that we can carry out a complete vitrectomy. Any residual gel will almost certainly be compressed by the tamponade and lose its water content, thus creating effectively a larger cavity and thus an under fill.[8] In practice, therefore, the fill of the vitreous cavity is almost always less than 100%; the silicone oil bubble is surrounded (inferiorly and possibly posteriorly) with a film of aqueous.

This film of aqueous might be important because if it is too thin, there may not be sufficient water to maintain ionic exchange. This may, in turn, give rise to hyperpolarisation of the Muller cells and apoptosis from excitoxicity.[9] At least this was one of the speculated mechanism for retinal changes associated with long-term tamponade. This mechanisms is also invoked to account for 'unexplained' visual loss after silicone oil removal.[10] Although perfluorocarbon liquids (PFCL) have been used for short-term tamponade for treating giant retinal tears, PFCL are usually removed after a short period of tamponade, for example 2 weeks, because of worry over its toxicity. In rabbit studies, retinal changes were observed after a few weeks and the histological changes were thought to be caused by the weight of PFCL and the effect of their pressure on the retina.[11] So when it came to the design of HSO, consideration was given as to how heavy it should be. The solubility of perfluorohexyloctane (F6H8) is limited, but clearly the more F6H8 is dissolved, the higher the specific gravity. The higher the specific gravity, the flatter is the profile of the bubble, and the more effective it is at displacing the aqueous, the greater the possibility of excitoxicity. In the end, a density of 1.06 was chosen as a commercial product for Densiron. Conventional silicone has a specific gravity of $0.97\,g/cm^3$. There are no published figures for the specific gravity of vitreous fluid after a vitrectomy, but it is likely to be close to $1.00\,g/cm^3$. So Densiron-68 might have a slightly greater difference in specific gravity, but it also has a slightly greater interfacial tension with water than conventional silicone. In the model eye chamber, we have shown that Densiron-68 has the same profile as conventional silicone oil. The assumption is that Densiron should physically behave like conventional silicone oil in terms of its ability to displace aqueous and its likelihood to cause retinal changes.

If Densiron and conventional silicone oil behave physically in a similar manner, would we have the same effectiveness when it is used in a real-life situation for which conventional silicone oil might be used? Densiron has been shown to be effective in a two-centred pilot study of 42 cases involving Rotterdam and Liverpool. Here we present our experience with using it for conventional indications such as PVR and for extended indications such as re-do operations and RD without PVR but complex arrangements of multiple, inferior and posterior retinal breaks.

Material

Densiron 68 (FLUORON GmbH, Neu-Ulm, Germany) is a heavier-than-water tamponade agent, often referred to as HSO. Its 'heaviness' is derived from one of its components F6H8 (specific gravity $1.35\,g/cm^3$) that makes up 30.5% of its volume.

The resulting physical properties are as follows: specific gravity $1.06\,g/cm^3$ at 25°C; viscosity 1400 mPas at 25°C; its refractive index is 1.387; and its interfacial tension against water is 40.82 mN/m.

Methods

We present a prospective interventional non-comparative case series of 122 eyes of 121 consecutive patients recruited from January 2004 till August 2006. It was designed as an ongoing prospective audit on the use of Densiron in a routine clinical environment. We built upon the same methodology as in our two-centred pilot study, which received the approval of the institutional review boards of both institutions. Densiron 68 HSO was used in all cases both as a primary and as a subsequent procedure.

Main outcome measures

Our primary end point was anatomical re-attachment of the retina. Success was defined as retinal re-attachment in the absence of any tamponade agent with one or multiple retinal operations. The secondary end point was to record the visual function and any complications arising from surgery.

Inclusion and exclusion criteria

Inclusion criteria consisted of PVR, complicated RD including patients who have had failed previous retinal surgery, RD arising from posterior or inferior retinal breaks, and an inability of the patient to posture. In the presence of PVR, patients with superior and inferior breaks were included. We excluded Densiron use for other indications such as choroidal haemorrhage and perforating injury as well as the inability of the patient to give consent.

Audit protocol

The protocol consisted of a minimum of eight clinic visits: baseline, HSO-surgery, 1 week, 1 month post-HSO,

the removal of oil, and 1 week, 1 and 3 months postoperatively. LogMar acuity was obtained with pinhole vision, IOP, corneal, anterior chamber, lens, posterior lens capsule, and retinal status as well as the degree of oil fill, the presence of emulsification, and other averse events were obtained at follow-up visits No. (1,3,4,6–8). Further breaks localisation, PVR—stage, and all surgical complications were recorded at episodes 2 and 5. Surgical notes were supplemented by retinal drawings. We continued to use the pro forma used in our pilot study, which was specifically designed to record unscheduled appointments or additional interventions, as the observer is forced to positively confirm or deny the presence of any complications.

Postoperative posture

It is our routine clinical practice to posture our patients for about 10–14 days. After being initially postured supine for 3 h, those patients with inferior retinal breaks confined to the inferior 4 o'clock hours were not required to posture; those with retinal breaks above 4 and 8 o'clock were postured lying on their sides; those with retinal breaks on both temporal and nasal sides were postured alternately lying on the left and right sides.

Results

Basic demographics

The mean age of the patients was 59.9 years (± 19.6). There were 72 male and 49 female patients. There were 65 right eyes and 57 left eyes. One patient had bilateral surgery.

Previous interventions

Seventy-seven patients (63.1%) had previous retinal surgery with a mean of 1.2 operations ± 0.43. Sixty-seven had one previous operation, 13 had two previous operations, and one had three previous operations. Ten patients had previous Cryo and Buckle surgery and 75 had previous vitrectomies. Of these vitrectomies, 30 had previous gas (C3F8 12%) and 45 had conventional silicone oil. In 12 cases, the silicone oil had been removed before, and in the remaining 33 cases the retinal re-detachment occurred with silicone oil *in situ*. For the other 45 patients, HSO was used at the first operation.

Indications

Indications were inferior retinal breaks in 70 cases (57%) and PVR was present in 80 (65%) cases, 48 (60%) of which were either stages CP1 or CP2. These diagnoses did not exclude one another and patients often presented with both findings. There were four cases of trauma and six macular relocation patients who developed a RD.

The extent of the detachments was 2.21 quadrants(± 1.07) with macular involvement in 66 cases (54%). One hundred and nine retinal breaks were located at 3–9 o'clock or below, the majority being at 6 o'clock.

Lens status

At baseline, 61 (50%) patients were phakic, 52 (42.6%) were pseudophakic (posterior chamber lens PCIOL), 3 (2.4%) had an anterior chamber lens (ACIOL), and 5 (4%) were aphakic.

Anatomical results

Eighty-seven (71.3%) patients achieved retinal re-attachment with one retinal operation and no tamponade, 102 (83.6%) achieved retinal re-attachment with more than one operation and no tamponade, and 112 (91.3%) patients achieved flat retina with tamponade *in situ* (Table 1).

A total of 35 patients re-detached. Eighteen patients re-detached with Densiron *in situ*, 11 at 1 week, and 7 at 1 month postoperatively. Seven patients had macular involvement. All detachments were superior under heavy oil. Seventeen patients re-detached after Densiron had been removed.

Of the total of 35 patients with re-detachments, we managed to re-attach the retina and eventually the tamponade was removed in 15 cases. In 10 patients, retinal re-attachment was achieved under tamponade and in 10 cases the retina could not be fully re-attached (Table 2).

Of those, five (4%) suffered hypotony/phthisis, three patients were lost to follow-up before the 3-month period, and one patient died.

Table 1 Anatomical results at 3 months following heavy oil removal

Flat retina with one operation and no tamponade	87 (71.3%)
Flat retina with more than one operation and no tamponade	102 (83.6%)
Flat retina with tamponade	112 (91.8%)

Table 2 Further management of the re-detachments

Further operations	*Numbers*	*Total*
Retinal re-attachment no tamponade	11 oil + 4 gas	15
Retinal re-attachment with tamponade	5 oil + 5 HSO	10
Retina not attached with tamponade	6 oil + 4 HSO	10
Sum		35

Abbreviation: HSO = heavy silicone oil.

The mean duration of Densiron left *in situ* was 135 days (±73.2; range 35–405 days).

Functional results

Visual acuity rose from 1.38 LogMar (±0.87) to 1.06 LogMar (±0.83) at the primary end point of 3 months (Table 3). The difference was significant using the two-tailed *t*-test ($P = 0.007$). At the last recorded clinic visit, vision rose to 0.93 LogMar (±0.92) and the mean duration of follow-up was 10.44 months (range 3–30 months) with the last recorded visit carried forward.

Complications

Cataract formation

At the last postoperative visit, only 7 (5.7%) patients were phakic, 94 (77%) had a PCIOL, 5 (4%) had an ACIOL, and 3 (2.4%) were aphakic.

Raised intraocular pressure

At baseline, 11 patients had an intraocular pressure (IOP) greater than 21 mmHg and 5 more patients showed IOP higher than 30 mmHg. Nine patients received treatment for glaucoma. At first week postoperative, 29 (23.7%) patients developed a postoperative IOP greater than 21, and in addition 14 (11.5%) patients showed an IOP of more than 30 mmHg. They were medically controlled with an average of 1.87 antiglaucomatous drops. There was a steady decrease in the incidence of high pressure towards the end of the surveillance period with eight patients showing more than 21 mmHg and only one patient with persistent IOP > 30 mmHg at 3 months following heavy oil removal (Table 4). No patient required drainage surgery.

Intraocular inflammation

Inflammation was mainly mild and tended to be noticed at the 1-week follow-up visit. Eleven patients showed moderate and one showed severe inflammation (Table 5).

Dispersion/emulsification of Densiron

Visible emulsification increased with time, even after Densiron removal (Table 6). About 28 (23%) patients showed emulsification 1 month after oil removal, 14 (11%) of which were apparent in the anterior chamber.

Table 3 Visual acuity [LogMar] at end point

Vision	*Number*	*Percentage*
20/20 or better	7	5.7
20/40–20/20	34	27.9
20/200–20/40	48	39.3
Below 20/200	33	27.1
Sum	122	100

Table 5 Intraocular inflammation: (+ mild; ++ moderate; +++ severe)

	Mild	*Moderate*	*Severe*
Inflammation	+	++	+++
Baseline:	3	2	1
1 week HSO	37 (30%)	11 (9%)	1 (1%)
1 month HSO	25 (20%)	2 (2%)	2 (2%)
1 week RHO	27 (22%)	6 (5%)	0
1 month RHO	15 (12%)	5 (4%)	0
3 months RHO	8 (7%)	1 (1%)	0

Abbrevitaions: HSO = heavy silicone oil; RHO = removal of heavy oil.

Table 6 Total number of patients showing visible emulsification

	Anterior chamber	*Total emulsification*
Baseline:	0	0
1 week HSO	6 (5%)	16 (13%)
1 month HSO	11 (9%)	13 (11%)
1 week RHO	12 (10%)	16 (13%)
1 month RHO	14 (11%)	28 (23%)
3 months RHO	16 (13%)	23 (19%)

Abbreviations: HSO = heavy silicone oil; RHO = removal of heavy oil.

Table 4 Intraocular pressure

	Visit	*<21 mmHg*	*<30 mmHg*	*Treatment*	*Number of drops*
√	Baseline:	11 (9%)	5 (4%)	9	1.1
√	1 week HSO	29 (24%)	14 (13%)	14	1.87
√	1 month HSO	18 (15%)	9 (7%)	16	1.62
√	1 week RHO	9 (7%)	2 (2%)	5	1.4
√	1 month RHO	8 (7%)	2 (2%)	8	1.5
√	3 months RHO	8 (7%)	1 (1%)	8	1.8

Abbrevitaions: HSO = heavy silicone oil; RHO = removal of heavy oil.

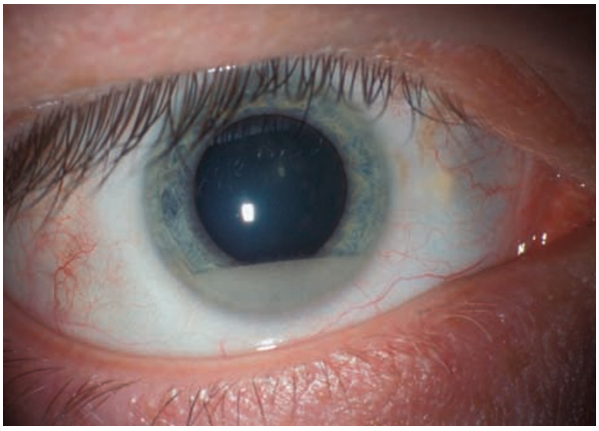

Figure 1 Pseudohypopyon due to emulsified heavy oil.

The patient with the maximal amount of emulsification (pseudohypopyon) is shown in (Figure 1). In no patient did the amount of emulsification interfere with the visibility of the retina.

Other complications

There was one case of vitreous haemorrhage and one decompensated corneal graft due to silicone oil keratopathy. There were no cases of endophthalmitis.

Discussion

Densiron is a solution of F6H8 in silicone oil. Although F6H8 was found to be safe and well tolerated in rabbits, in humans it is associated with retrolental and epiretinal membranes and inflammation.[12] Our group was the first to identifiy CD68+ foreign body giant cell reaction in epiretinal membranes associated with F6H8 used as a long-term tamponade, and we postulated that the inflammation reaction was related to emulsification.[13] In other situations, seemingly biologically inert and compatible substances such as PTFE and silicone can cause intense inflammation when injected into the body as dispersed droplets. It is this inflammation that is exploited to cause fibrosis around the urethra to treat post-prostatectomy incontinence.[14]

The propensity of a tamponade agent to disperse in aqueous is dependent on its viscosity. F6H8 has a low viscosity and therefore readily disperses into small droplets. It has been shown that small droplets of F6H8 and silicone stabilised by surfactants can activate[15] macrophages. By mixing F6H8 with conventional silicone oil, the resultant solution would have a high viscosity and therefore much less propensity to disperse. We had reported in our pilot series that Densiron was safe. In this paper, we audit its routine use for PVR and other complicated RD.

In our pilot study, the success rate with one operation using Densiron was 81% and with further surgery, 93%. All tamponade agents were removed in 90% of patients at the end of the study. Visual acuity improved from mean logMAR of 1.41 (SD, 0.64) to 0.94 (SD, 0.57), $P = 0.001$. Our current success rate was lower in both the primary as well as the final re-attachment rates. The difference between the pilot and current series might be due to the fact that we, encouraged by our initial high success rate, were using Densiron for increasingly difficult cases. The primary re-attachment rate reported by others is also highly variable; it ranges from 92.3% by Tognetto *et al*[16] and 45.8% by Sandner *et al*.[17] Such differences might again be attributable to a different case-selection. Sander *et al*, for example, applied Densiron exclusively to cases that had failed previous retinal surgery. Although the anatomical success rates could be different, the complication rates from different series were much the same. The impression is that Densiron and conventional silicone oil have similar complication rates in clinical use.

The availability of a long-term tamponade that is heavier than water on its own does not justify its use. There are still concerns over its safety and there are debates over its indications. Martinez-Castillo *et al* have demonstrated that it is possible to treat retinal breaks without tamponade at all[18] and Tanner *et al* demonstrated that inferior retinal breaks can be treated by vitrectomy and gas but without scleral buckling.[19] These are, of course, selected cases. It might be argued that PVR cases and complicated RD required prolonged tamponade. However, despite the findings of the silicone oil study,[20] the precise indications for when to use long-acting gases and when to use conventional silicone oil remain unclear. Equally, in the presence of PVR, it is possible to treat cases with inferior retinotomy using conventional silicone oil, attesting to the fact that conventional silicone can be effective for inferior breaks[21] and PVR. The use of HSO and conventional silicone oil, however, do not have to be mutually exclusive. We have shown in a small series that sequential use of conventional silicone and Densiron can be effective.[22]

The role of HSO is therefore not yet clinically defined. Because Densiron sinks and therefore displaces the proliferative aqueous environment superiorly, this leads to the hypothesis that it might be more effective than silicone oil in cases of PVR where there are no breaks in the superior 4 o'clock hours. This hypothesis is being tested by the Heavy Silicone Study (HSO),[23] an international randomised control trial led by Cologne. The rigours of an RCT will best reveal the safety profile of Densiron. It is in the context of this trial that we intend to concentrate our use of Densiron in the future.

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