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Improved Outcomes with Heavy Silicone Oil in Complex Primary Retinal Detachment

A Large Multicenter Matched Cohort Study

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Purpose: To establish whether Densiron 68, a heavier-than-water endotamponade agent, is an effective alternative to conventional light silicone oil in primary rhegmatogenous retinal detachment (RD) surgery for eyes with inferior breaks in the detached retina and severe proliferative vitreoretinopathy (PVR).

Design: Cohort study of routinely collected data from the European Society of Retina Specialists and British and Eire Association of Vitreoretinal Surgeons vitreoretinal database between 2015 and 2022.

Participants: All consecutive eyes that underwent primary rhegmatogenous RD surgery using Densiron 68 or light silicone oil as an internal tamponade agent.

Methods: To minimize confounding bias, we undertook 2:1 nearest-neighbor matching on inferior breaks, large inferior rhegmatogenous RDs, PVR, and, for visual analyses, baseline visual acuity (VA) between treatment groups. We fit regression models including prognostically relevant covariates, treatment−covariate interactions, and matching weights. We used g-computation with cluster-robust methods to estimate marginal effects. For nonlinear models, we calculated confidence intervals (CIs) using bias-corrected cluster bootstrapping with 9999 replications.

Main Outcome Measures: Presence of a fully attached retina and VA at least 2 months after oil removal.

Results: Of 1061 eyes enrolled, 426 and 239 were included in our matched samples for anatomic and visual outcome analyses, respectively. The primary success rate was higher in the Densiron 68 group (113 of 142; 80%) compared with the light silicone oil group (180 of 284; 63%), with an adjusted odds ratio of 1.90 (95% CI, 1.63−2.23, $P < 0.001$). We also observed a significant improvement favoring Densiron 68 of −0.26 logarithm of the minimum angle of resolution (logMAR) in postoperative VA between the 2 groups (95% CI, −0.43 to −0.10, $P = 0.002$). The anatomic benefit of using Densiron 68 in eyes with inferior retinal breaks and large detachments was more pronounced among eyes with PVR grade C. We found no evidence of visual effect moderation by anatomic outcome or foveal attachment.

Conclusions: Densiron achieved higher anatomic success rates and improved visual outcomes compared with conventional light silicone oil in eyes with inferior retinal pathology and severe PVR.

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Retinal detachment (RD) is a complex condition that requires timely and effective intervention to prevent permanent vision loss.[1,2] Although gas tamponades are the preferred option in treating rhegmatogenous retinal detachments (RRDs),[3] the use of light silicone oil (LSO) tamponade is sometimes warranted in cases with specific characteristics, including large and multiple breaks, or the presence of proliferative vitreoretinopathy (PVR).[4,5] Various brands of LSO are approved by regulatory agencies worldwide, including in the United States, European Union, United Kingdom, Canada, China, Russia, and Japan. Light silicone oils, made from polymerized siloxane (PDMS) with a specific gravity of 0.97 g/cm^3 (lower than water) at 25°C (77°F), have limited effectiveness in supporting the inferior retina and closing inferior breaks unless strict posturing is observed.[5] The introduction and use of heavier-than-water tamponade agents such as heavy silicone oil (HSO) have been advocated for cases of inferior RD with inferior retinal breaks, especially when severe PVR is

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present.[4,6] Because these features are known to be associated with increased rates of anatomic failure and postoperative PVR, choosing the optimum tamponade is critically important.

Densiron 68 (hereon referred to as "Densiron") (Fluoron GmbH) is an HSO consisting of 69.5% 5000 centistokes (cSt) PDMS and 30.5% perfluorohexyloctane (F_6H_8) that has been proposed as an effective tamponade for inferior RDs due to its specific gravity of 1.06 g/cm^3 (higher than water).[4–7] However, concerns about its potential for emulsification and subsequent inflammation above the main oil bubble have been raised, with some hypothesizing that this could lead to increased rates of complications such as PVR and epiretinal membranes.[4,8] Its efficacy also has been questioned, with no clear benefit over LSOs shown to date.[9,10] Most published results center on patients undergoing revision surgery for RRD, with only limited data on individuals undergoing surgery for primary RRD with Densiron. Furthermore, phenotypic variation between RRD cases in published series has confounded results. Nevertheless, Densiron and Densiron Xtra, an improved formulation with Siluron Xtra (a PDMS mixture from Fluoron GmbH) instead of 5000 cSt PDMS to enhance emulsification resistance, have received approval for use in the European Union, United Kingdom, Canada, China, and Russia, but not in the United States or Japan.

To address the limitations of earlier studies, we investigated whether using Densiron as a tamponade after initial repair of primary RRD improves anatomic and visual outcomes in a large, population-based cohort matched and adjusted for inferior retinal pathology and PVR grade C (PVR-C). Our findings inform the choice of tamponade agents in these challenging cases.

Methods

Study Design and Participants

We analyzed routinely collected data from the European Society of Retina Specialists and the British and Eire Association of Vitreoretinal Surgeons vitreoretinal database, an online platform for anonymous collection and analysis of clinical and procedural data, ongoing since May 2012. This database includes primary RRDs in patients aged more than 16 years, excluding secondary RDs (e.g., vasoproliferative disorders, trauma, ocular dystrophies, uveitis, and syndromic pediatric RD), as well as cases of revision surgery. It focuses exclusively on primary outcomes and does not record reoperation results. The database conforms to the UK national RD dataset and uses standardized data collection fields.[11] As per UK guidance, data collection is classified as an audit for the purpose of service evaluation, so Institutional Review Board approval and informed consent are not required. However, we obtained approval from each participating Hospital Trust before data compilation and analysis, in line with national information governance procedures and adhering to the tenets of the Declaration of Helsinki. Data were recorded at the level of the operated eye immediately after the surgery and once more on completion of follow-up. The surgical procedure and selection of tamponade agent remained at the sole discretion of the operating surgeon.

Data Collection

We identified eyes that underwent primary RRD surgery with vitrectomy using LSOs of 1000, 2000, or 5000 cSt viscosity, or Densiron as an internal tamponade agent between May 2012 and December 2022. Despite variations in viscosity, LSOs are expected to provide similar retinal support, being composed of 100% polydimethylsiloxane (PDMS) with identical specific gravity and interfacial tension relative to water (40.0 mN/m).[12] To facilitate analysis, we treated these collectively as a single group. Our database included 10 cases using Oxane HD (69.5% 5000 cSt PDMS and 11.9% RMN3; Bausch + Lomb). However, because of different viscosities (Oxane HD 3 300 cSt vs. Densiron 1 349 cSt), interfacial tension (44.9 vs. 40.8 mN/m), and a lower specific gravity (1.02 g/cm^3),[12] we did not analyze these eyes with the Densiron-treated cases to avoid confounding. Inappropriate entries, such as revision surgery or secondary RDs, were also excluded. Figure 1 shows an overview of our selection criteria.

Data collected at baseline included age, sex, lens status, ocular co-pathology, best-corrected visual acuity (VA), grade of vitreous hemorrhage (VH), and anatomic features such as number, location, type, and extent of retinal breaks, RRD extent and foveal involvement, and presence and extent of PVR-C, defined as full-thickness retinal folds as per the Retina Society's classification system.[13] Of note, an RD drawing tool was linked to the diagnostic grading of anatomic features to facilitate data collection, allowing us to identify RD extent. Representative fundus drawings from both treatment arms of our sample are presented in Figure 2. We also extracted procedural details and postoperative data, including primary (anatomic) success and final best-corrected VA, for analysis. Patient identifiers were unavailable, so we could not incorporate these as covariates in our analyses. However, we estimate that less than 5% of our sample underwent bilateral RRD surgery during the study period. Although our database lacked a surgeon identifier for residents, minimal impact on results is expected, given that most centers have only 1 vitreoretinal surgeon in training supervised by an attending surgeon.

Outcomes

Our database defines anatomic success as the successful reattachment of the retina, followed by the removal of oil, and the presence of a fully attached retina at least 2 months after oil removal (and within 12 months of initial surgery). Eyes that had additional interventions to achieve reattachment after the original procedure including at the time of oil removal or that did not have oil removal within 12 months are classed as failure. Re-detachments at any point during or beyond this period are classified as failures, and the database outcomes are updated. Postoperative VA is only recorded once in the database: at the last clinical assessment. To avoid confounding by the immediate postoperative period, we stipulated that VA be clearly recorded at least 2 months after oil removal for visual outcome analyses. Where time from oil removal to last assessment was unavailable, we only included eyes with anatomic success in our visual analyses because this is, by definition, at least 2 months after oil removal.

Statistics

We conducted all analyses in R version 4.2.1 (The R Foundation, Vienna, Austria). Before outcome modeling, we created 2 samples for anatomic and visual analyses, matched for prognostically significant covariates to mitigate confounding bias in the effect estimate (Fig 1). For anatomic analyses, we matched on the presence and position of inferior breaks, the presence and extent of inferior RD, as well as the presence and extent of PVR-C. For visual

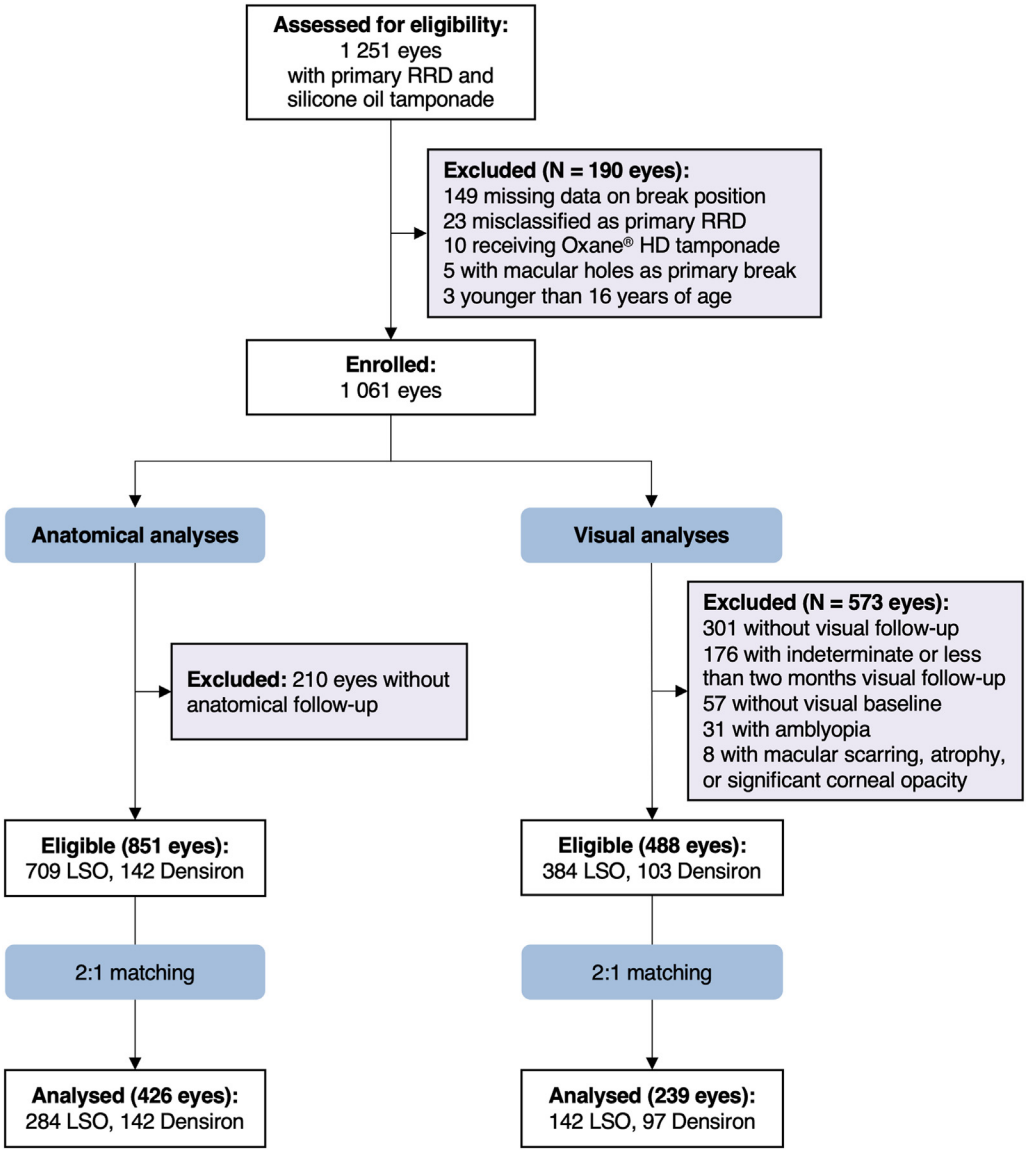

Figure 1. Flowchart showing selection criteria for matching and analysis. LSO = light silicone oil; RRD = rhegmatogenous retinal detachment.

analyses, we also matched on baseline VA. We did not match on anatomic or visual outcome for any analysis. We explored various distance matching methods and specifications, achieving optimal balance and precision through 2:1 nearest-neighbor matching without replacement on the scaled Euclidean distance. We confirmed satisfactory covariate balance in our matched samples by visualizing standardized mean differences (MDs) (Fig S3, available at www.aaojournal.org) as well as variance ratios and Kolmogorov–Smirnov test statistics (not presented). We also examined the exponents and interactions of covariate distributions (Figs S4 and S5, and Appendices 1 and 2, available at www.aaojournal.org).

To model anatomic and visual outcomes in our matched samples, we used multivariable logistic and linear regressions, respectively, with treatment-by-covariate interactions and matching weights. We adjusted for age, sex, foveal attachment at baseline, inferior and noninferior RD extents, PVR-C extent, VH grade, relaxing retinotomy extent, and drainage retinotomy presence, as well as inferiority of the lowest, centermost, and highest breaks in all analyses (Fig 2). For visual analyses, we also adjusted for baseline VA and postoperative lens type. In cases where postoperative lens type was missing (126 eyes), we imputed the baseline lens type.

We were interested in comparing the average outcomes of eyes treated with Densiron versus those that would have occurred if they received LSO (the average treatment effect in the treated) to address whether Densiron should continue to be used in populations that resemble ours. To do this, we estimated marginal (population-averaged) effects using g-computation, with cluster-robust standard errors to account for dependence between matched pairs.[14,15] Likewise, we assessed potential variations in treatment across different clinical characteristics in subgroup and moderation analyses. For all anatomic analyses, we refined confidence intervals (CIs) using the bias-corrected and

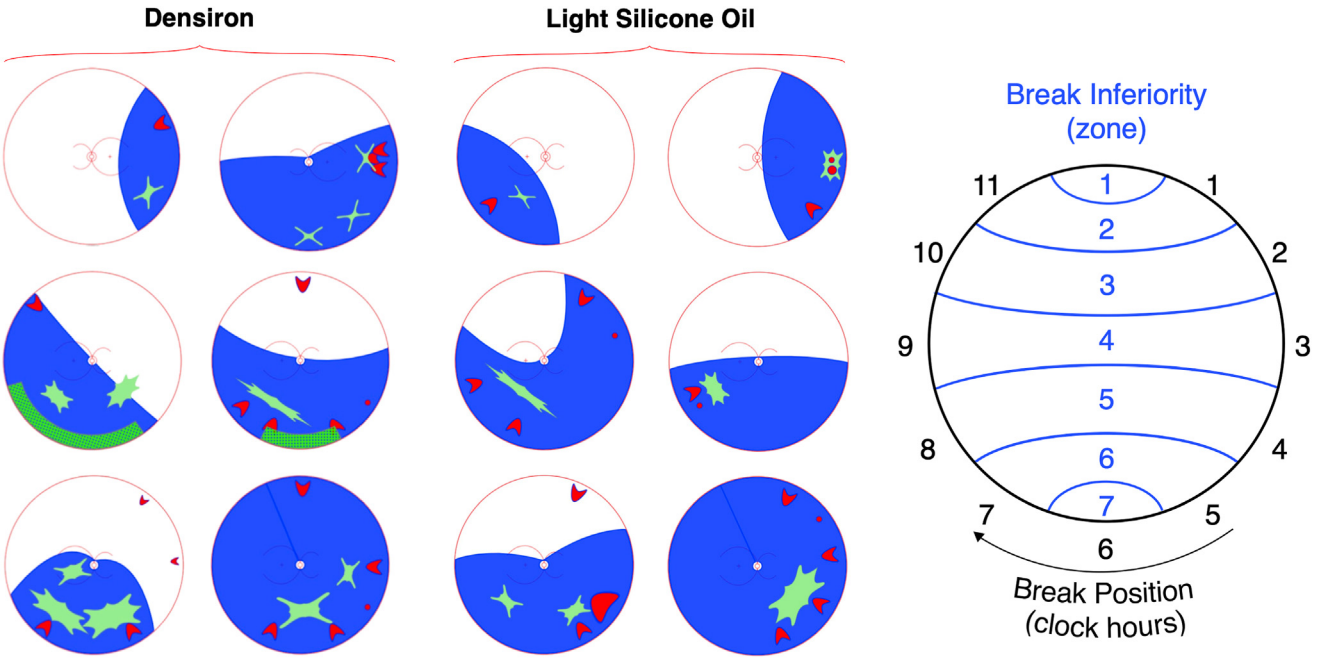

Figure 2. Retinal drawings from our matched sample showing diverse clinical presentations treated with Densiron or light silicone oil. These encompass eyes with multiple U-tear or round hole breaks, varied proliferative vitreoretinopathy positions and extent, and large or funnel detachments. There were several instances of Densiron use in the context of superior breaks and, conversely, of light silicone oil use for inferior breaks. The schematic on the right showcases our development of a continuous inferiority scale for the highest, centermost, and inferior breaks that were adjusted in our analyses. This involved partitioning the retinal break position into 7 zones, irrespective of laterality.

accelerated cluster bootstrap with 9999 replications, which is considered more accurate than the standard approach.[15] Appendix 3 shows further details on our statistical methods (available at www.aaojournal.org).

Results

Descriptive Statistics

We obtained data on 1251 eyes (9%) with primary RRD and silicone oil tamponade from a total database of 13 900 eyes at the time of data extraction. We excluded 149 eyes with missing data on break position, 23 eyes that were misclassified as primary RRD, 10 eyes involving tamponade with Oxane HD (Bausch & Lomb), 5 eyes with macular holes as the primary retinal break, and 3 eyes of patients aged less than 16 years (Fig 1). There were no eyes with missing values for inferior RD extent or PVR-C presence/extent. For anatomic analyses, we additionally excluded 210 eyes without postoperative primary outcome data (Fig 1). Furthermore, for visual analyses, we excluded another 301 eyes with missing postoperative VA, 176 eyes whose postoperative VA was not clearly measured at least 2 months after oil removal, 57 eyes without baseline VA, 31 eyes with a history of amblyopia, and 8 eyes with macular scarring, atrophy, or significant corneal opacity at presentation (573 total exclusions; Fig 1). We found no relationship between the type of tamponade agent and missing outcome data ($P = 0.17$ and 0.76 for anatomic and visual outcome data, respectively).

Our matching method successfully achieved similar covariate distributions between treated and control groups, as demonstrated by standardized MDs below 0.1 for covariates (Fig S3) as well as their interactions and exponents (Figs S4 and S5, available at www.aaojournal.org). For anatomic outcome analyses, there were a total of 851 eyes remaining after exclusions. Through our matching process, we obtained 426 matched eyes (143 Densiron and 286 LSO recipients). Of 488 eyes available for visual outcome analyses, matching resulted in 239 matched eyes (97 Densiron and 142 LSO). Baseline characteristics between groups were similar across both samples as illustrated by Tables 1 and S2 (available at www.aaojournal.org).

In our unmatched sample, the highest and lowest retinal breaks of eyes receiving Densiron were commonly found *below* 2−10 o'clock (107 [58%] of the highest and 175 [94%] of the lowest retinal breaks of 186 eyes), and *at or above* 2−10 o'clock in those receiving LSO (704 [80%] and 332 [38%] of 875 eyes, respectively; Tables S2 and S3, available at www.aaojournal.org). However, after matching for inferior retinal pathology, the distribution of lowest retinal break position was near identical between the 2 groups (Tables S2 and S3, and Fig S6, available at www.aaojournal.org). Although the lowest retinal break was at or above 2−10 o'clock in 6% (8 of 142) of the eyes receiving Densiron in our matched sample, these cases presented other possible indications for HSO tamponade: 6 with PVR-C, 4 with retinotomies, and all with inferior RDs.

In the matched sample for anatomic outcome analysis, patients had a mean age of 64 years (standard deviation [SD], 14), and 290 of 426 (68%) were male. The mean duration of oil tamponade was 124 days (SD, 108). In addition to the clinical characteristics presented in Table 1, there were also the following:

- 360 of 426 eyes (85%) with inferior breaks at 4−8 o'clock and an inferior RD of ≥ 3 clock-hours, among which 147 (41%) also had PVR-C

- 194 of 426 eyes (46%) with inferior breaks at 4−8 o'clock and an inferior RD of ≥ 6 clock-hours, with 93 (48%) of these cases also presenting with PVR-C

Univariable Analyses

The primary success rate for RRD repair was 73% (617 of 851 eyes) among the unmatched eyes with available data. Eyes treated with Densiron achieved an 80% success rate (113 of 142 eyes), surpassing those treated with LSO at 71% (504 of 709 eyes; $P = 0.049$). After matching for inferior retinal pathology and PVR-C, the overall anatomic success rate was 69% (293 of 426 eyes). Densiron outperformed LSO, with success rates of 80% (113 of 142 eyes) and 63% (180 of 284 eyes), respectively ($P = 0.001$; Fig 7).

Among 488 eligible eyes for visual analyses, the 103 receiving Densiron demonstrated improved postoperative VA at a mean of 0.51 logarithm of the minimum angle of resolution (logMAR) (SD, 0.47), in contrast to the 384 eyes treated with LSO at 0.70 logMAR (SD, 0.55). Adjusting for baseline VA only, Densiron use correlated with a postoperative VA improvement of −0.14 logMAR (95% CI, −0.26 to −0.03, $P = 0.015$) compared with LSO in this cohort. After matching for inferior retinal pathology, PVR-C, and baseline VA, resulting in 239 paired eyes, postoperative VA remained superior in the Densiron group at 0.52 logMAR (SD, 0.48) compared with 0.72 logMAR (SD, 0.50) for LSO recipients (Fig 7). Adjusted for baseline VA only, this translates to a −0.18 logMAR improvement with Densiron compared with LSO (95% CI, −0.30 to −0.06, $P = 0.004$). In this matched sample, 4 of 97 eyes (4%) receiving Densiron experienced a visual deterioration of at least 0.2 logMAR, contrasting with 16 of 142 eyes (11%) receiving LSOs ($P = 0.09$).

In our matched sample for visual analyses (matched on baseline VA, inferior retinal pathology, and PVR-C), all 239 eyes had documented anatomic outcomes. However, only 8 (3%) experienced anatomic failure: 4 with Densiron (4%) and 4 with LSO (3%). This discrepancy in success rates compared with our matched sample for anatomic analyses is due to different selection criteria. For visual analyses, we required final postoperative VA recorded at least 2 months after oil removal to avoid confounding by the immediate postoperative phase. To maintain an adequate sample size, where the timing of VA measurement relative to oil removal could not be ascertained (854 of 1 061 eyes; 80%), we also included eyes with documented anatomic success (i.e., attached at least 2 months after oil removal) and a recorded postoperative VA. In the resulting matched sample, the timing of VA assessment after oil removal was available in 76 of 239 cases (32%), at a median of 2.9 months (IQR 2.4−5.7) in the Densiron group, and 3.7 months (IQR 2.8−5.5) in the LSO group ($P = 0.19$), as shown in Figure S8 (available at www.aaojournal.org).

Multivariable Analyses

The adjusted odds ratio (OR) of Densiron on anatomic success was 1.90 (95% CI, 1.14−3.16, $P = 0.014$) compared with LSOs in our matched sample of 426 eyes for anatomic analyses. Through bootstrapping, we refined the 95% CIs for anatomic success with Densiron to 1.63 to 2.23 ($P < 0.001$). The adjusted MD of Densiron on postoperative VA was −0.26 logMAR (95% CI, −0.43 to −0.10 $P = 0.002$) compared with LSOs in our matched sample of 239 eyes for visual analyses.

Subgroup and Moderation Analyses

Effect of PVR on Anatomic Outcome. Subgroup analyses in our sample for anatomic analyses (426 eyes), unstratified by inferior retinal pathology, showed that Densiron use was associated with higher odds of anatomic success relative to LSOs in the 189 (44%) eyes with PVR-C (OR, 1.22, 95% CI, 1.07−1.36, $P = 0.002$) but not in the 237 (56%) eyes without PVR-C (OR, 1.07, 95% CI, 0.95−1.20, $P = 0.26$). Moderation analysis confirmed a similar or higher efficacy of Densiron relative to LSOs in the presence of PVR-C (OR, 1.13, 95% CI, 0.99−1.28, $P = 0.043$).

In subgroup analyses of eyes with inferior breaks 4−8 o'clock and inferior RD extent ≥ 3 clock hours (360 of 426 eyes; 85% of sample), Densiron use was associated with a significant increase in the odds of anatomic success in the 147 eyes (41%) that also had PVR-C (OR, 1.27, 95% CI, 1.11−1.44, $P < 0.001$), but not in the 213 eyes (59%) without PVR-C (OR, 1.07, 95% CI, 0.95−1.20, $P = 0.29$), compared with LSO. Moderation analysis confirmed that eyes with inferior retinal pathology that also had PVR-C were more likely to benefit than those that did not (OR, 1.19, 95% CI, 1.04−1.34, $P = 0.005$).

Effect of Anatomic Outcome and Foveal Status on Visual Outcome. Subgroup analyses in our sample for visual analyses (239 eyes) demonstrated that Densiron achieved similar or superior efficacy over LSO in the 231 cases (97%) of anatomic success (MD −0.27 logMAR, 95% CI, −0.43 to −0.10, $P = 0.001$). Although only 8 eyes (3%) had anatomic failure in this sample, we can rule out with 95% certainty a clinically relevant visual deterioration of greater than 0.1 logMAR in this sample (MD −0.20 logMAR, 95% CI, −0.48 to 0.08, $P = 0.16$). We observed no evidence of visual effect moderation by anatomic outcome ($P = 0.54$).

Densiron was associated with significant postoperative VA benefit over LSO irrespective of baseline foveal attachment (51 of 239 eyes [21%]; MD −0.40 logMAR, 95% CI, −0.65 to −0.15, $P = 0.002$) or detachment (188 of 239 eyes [79%]; MD −0.22 logMAR, 95% CI, −0.41 to −0.04, $P = 0.020$), with no evidence of effect moderation ($P = 0.24$).

Discussion

Our study is the largest and one of the most comprehensive multicenter investigations to date on the use of HSO tamponade agents for primary RRD repair. After matching for inferior retinal breaks, extent of inferior RD, and PVR-C, eyes treated with Densiron exhibited improved anatomic and visual outcomes when compared with those receiving LSO in our sample, holding all other prognostically significant covariates and treatment−covariate interactions constant. Our findings suggest that Densiron use is associated with near-doubling of the odds of anatomic success in a single surgery (OR, 1.90, 95% CI, 1.63−2.23, $P < 0.001$) in this difficult-to-treat population. Subgroup and moderation analyses revealed that the apparent benefits of Densiron use were primarily driven by eyes with both inferior retinal pathology and PVR-C that had a 19% increase in the odds of anatomic success compared with eyes with inferior retinal pathology but no PVR-C (95% CI, 1.04−1.34, $P = 0.005$). The nearly identical covariate distributions in our matched dataset for anatomic analyses (as shown in Table 1 and Fig S3) indicate the consistent and unbiased nature of our estimates, suggesting they are less susceptible to model misspecification and closer to capturing the true treatment effect. By incorporating pair membership into our analysis, our results are also less vulnerable to unobserved confounders.[16]

In a separate sample matched on baseline VA as well as inferior retinal pathology and PVR-C, Densiron use was

Table 1. Baseline Characteristics in the Anatomic Outcome Analysis Sample after Matching

Variable	Total N (%)	Levels	LSO (N = 284)	Densiron (N = 142)	P
Age, yrs	426 (100)	Mean (SD)	63.3 (14.1)	64.4 (13.7)	0.42
Sex	426 (100)	Female	93 (32.7)	43 (30.3)	0.69
		Male	191 (67.3)	99 (69.7)	
Spherical equivalent refraction, D	105 (24.6)	Mean (SD)	−1.7 (6.0)	−0.8 (4.1)	0.28
Baseline VA, logMAR	375 (88.0)	Mean (SD)	1.7 (0.8)	1.3 (0.9)	<0.001*
Baseline lens status	426 (100)	AC IOL	1 (0.4)	0 (0.0)	0.29
		Aphakic	2 (0.7)	3 (2.1)	
		PC IOL	99 (34.9)	58 (40.8)	
		Phakic	182 (64.1)	81 (57.0)	
Grade of VH at baseline†	426 (100)	Mean (SD)	0.2 (0.6)	0.1 (0.5)	0.19
Foveal attachment at baseline	426 (100)	On	47 (16.5)	32 (22.5)	0.17
		Off	237 (83.5)	110 (77.5)	
Largest break type	426 (100)	Not found	0 (0.0)	0 (0.0)	0.037
		U-tear	234 (82.4)	122 (85.9)	
		Outer leaf break	12 (4.2)	11 (7.7)	
		GRT	38 (13.4)	9 (6.3)	
Inferiority of lowest break, clock-hours‡	426 (100)	Mean (SD)	6.1 (1.6)	6.0 (1.5)	0.58
Inferior breaks at 4−8 o'clock	426 (100)	No	34 (12.0)	17 (12.0)	0.99
		Yes	250 (88.0)	125 (88.0)	
Inferior breaks at 5−7 o'clock	426 (100)	No	73 (25.7)	30 (21.1)	0.36
		Yes	211 (74.3)	112 (78.9)	
Total RD extent, clock-hours	426 (100)	Mean (SD)	8.8 (3.0)	6.8 (2.6)	< 0.001
Inferior RD extent, clock-hours	426 (100)	Mean (SD)	5.0 (1.3)	5.0 (1.2)	
Inferior RD ≥ 3 clock-hours	426 (100)	No	12 (4.2)	6 (4.2)	0.99
		Yes	272 (95.8)	136 (95.8)	
Inferior RD ≥ 6 clock-hours	426 (100)	No	129 (45.4)	73 (51.4)	0.29
		Yes	155 (54.6)	69 (48.6)	
PVR-C at baseline	426 (100)	No	156 (54.9)	81 (57.0)	0.76
		Yes	128 (45.1)	61 (43.0)	
Antero-posterior PVR-C extent, clock-hours	426 (100)	Mean (SD)	1.3 (2.0)	1.2 (1.9)	0.66
Relaxing retinotomy	426 (100)	No	267 (94.0)	134 (94.4)	0.99
		Yes	17 (6.0)	8 (5.6)	
Drainage retinotomy	426 (100)	No	230 (81.0)	101 (71.1)	0.029
		Yes	54 (19.0)	41 (28.9)	
Scleral buckle	426 (100)	No	274 (96.5)	142 (100)	0.05
		Yes	10 (3.5)	0 (0.0)	
Symptom duration, days	233 (54.7)	Mean (SD)	37.8 (57.4)	33.7 (60.8)	0.26
Oil duration, days	260 (61.0)	Mean (SD)	131.8 (119.9)	112.4 (83.8)	0.37

AC = anterior chamber; D = diopters; GRT = giant retinal tear; IOL = intraocular lens; logMAR = logarithm of the minimum angle of resolution; LSO = light silicone oil; PC = posterior chamber; PVR = proliferative vitreoretinopathy; RD = retinal detachment; SD = standard deviation; VH = vitreous hemorrhage.

Null hypothesis statistical tests using Kruskal−Wallis test for continuous data and chi-square test for categorical data.

*Baseline visual acuity (VA) was not a covariate in our anatomic analyses so was not matched in this sample to preserve sample size and balance the high-risk prognostic features of inferior retinal pathology and PVR-C. However, baseline VA was adjusted for in our visual analyses that were based on a distinct sample precisely matched on baseline VA in addition to inferior retinal pathology and PVR-C. Table S1 (available at www.aaojournal.org) shows an overview of the baseline characteristics of our visual outcome analysis sample.

†VH was graded on a 5-point scale based on the extent of blood obscuring the retina at initial assessment, ranging from no blood present in the vitreous (grade 0) to dense VH with no visible retinal details (grade 4).

‡Inferiority of the lowest retinal break was determined on a 7-point scale, whereby breaks at 12 o'clock were assigned a value of 1, breaks at 1 or 11 o'clock a value of 2, and so forth.

associated with significant benefit in postoperative VA, achieving an improvement of −0.26 logMAR (95% CI, −0.43 to −0.10 $P = 0.002$) compared with LSO (Fig 7). This corresponds to, with 95% certainty, at least a clinically relevant 1-line gain on the Snellen chart. The observed visual benefits of Densiron over LSO are probably due to the corresponding anatomic improvement, as indicated by our subgroup analysis showing the same postoperative VA improvement when only considering eyes with anatomic success (95% CI, −0.43 to −0.10, $P = 0.001$). Although there was no evidence of visual effect moderation by baseline foveal attachment ($P = 0.24$) or anatomic outcome ($P = 0.54$), the eyes in this matched sample had a high proportion of anatomic success (231 of 239 eyes; 97%), so our results may differ in populations with higher anatomic failure rates. It is worth noting that instances of visual loss associated with HSO use have been infrequent compared with LSO,[17,18] although the incidence of visual deterioration by at least 0.2 logMAR was comparable between Densiron and LSO recipients in our study.

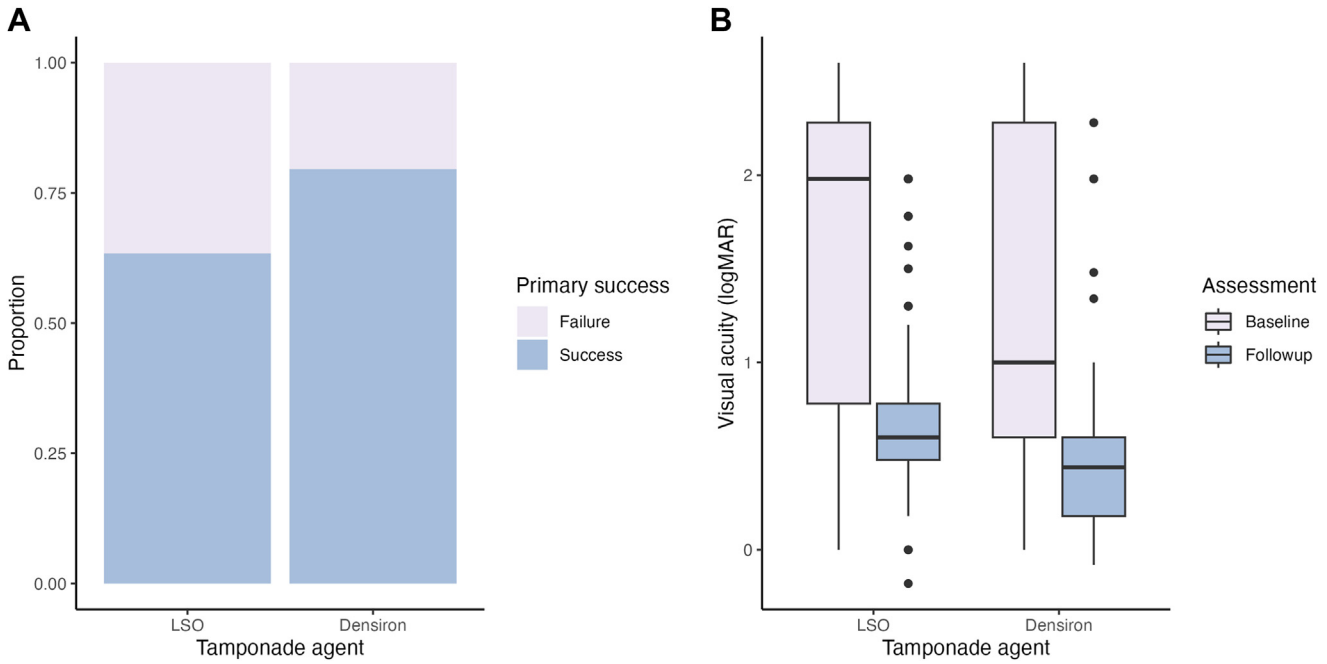

Figure 7. Anatomical (A) and visual (B) outcomes of retinal detachment repair in eyes receiving different tamponade agents. Anatomical success was defined as the successful reattachment of the retina, followed by the removal of oil, and the presence of a fully attached retina at least 2 months after oil removal and within 12 months of initial surgery. Postoperative visual acuity was recorded at least 2 months following oil removal. LSO = light silicone oil.

Consistent with previous observational research, we found that eyes treated with Densiron have a high primary success rate of 80% in primary RRD repair with inferior retinal pathology (Fig 7).[9,10,19–21] In a retrospective study of 33 eyes with primary inferior RRD and breaks between 4−8 o'clock, Romano et al[22] found that 91% of cases achieved primary retinal reattachment with 1 operation, and final anatomic success was achieved in 94% of cases. However, this study lacked a control group. Kocak and Koc[23] compared the effectiveness of Densiron and conventional LSO in the treatment of inferior retinal breaks in a prospective, randomized, nonmasked single-center study of 61 patients. Although their study found a higher retinal reattachment rate after oil removal at 3 months in recipients of Densiron (84%) compared with LSO (74%), this was not statistically significant, possibly due to a small sample size or the lack of controlling for relevant clinical and operative characteristics. Mean VA improved after Densiron use in both studies.[22,23] Davidson et al[9] conducted a retrospective study of 134 patients, almost all of whom had inferior RDs or breaks, and found a total final reattachment rate of 65% with Densiron, which was lower than our results. However, their study included patients who had previously undergone RRD repair, which may have reduced the likelihood of success. Because the study by Davidson et al did not include a control group, it remains unclear whether LSOs would have been associated with different outcomes in this population.

Our observed rates of anatomic success are also consistent with a retrospective comparative study by Moussa et al[10] involving 80 patients receiving Densiron and 179 receiving LSOs for primary RRD repair. They found that only 10% of cases had re-detachment under oil or required permanent oil tamponade at 6 months.[10] However, our study differs in that we identified significant anatomic and visual benefits of Densiron relative to LSOs, whereas they did not. Differences in study design, data collected and analyzed, visual end point used, and sample size may explain the discrepancies. Of note, Moussa et al[10] lacked data on inferior breaks or RDs and did not exclude revision, inflammatory, and pediatric cases. In terms of visual end point, we used postoperative VA adjusted for baseline VA, unlike Moussa et al,[10] who analyzed change from baseline, a metric that relies on several assumptions regarding the underlying data structure and has worse statistical power.[24,25] Bias in our dataset was minimized through prospective case ascertainment and data collection from multiple centers, complemented by robust statistical procedures. Furthermore, our focus on marginal effects (the same quantity estimated in randomized trials) reduces variance and is less vulnerable to covariate selection, so more likely to be consistent across different cohorts. Despite the differences in our findings, the authors did observe a lower retinectomy rate with Densiron compared with LSOs, indicating that HSOs may have anatomic benefits beyond primary success.

In the HSO Study by Joussen et al,[26] the efficacy of Densiron in complex RD was compared with standard LSOs in a randomized, masked, controlled, and multicenter investigation. This study focused on eyes with inferior RDs complicated by PVR-C or inferior giant retinal tears. The primary end points of complete retinal attachment before endotamponade removal at 12 months and final VA were found to be comparable between the 2 groups. The study, although of high quality, was terminated prematurely after

recruiting only 14% of its intended number of patients (93 of 660; 46 receiving Densiron), limiting its power to make definitive conclusions.[26,27] Additionally, the study had a high proportion of patients undergoing retina-affecting reoperations, and its complete list of eligibility criteria and admissible concomitant therapies may not be practical for routine practice. The authors concluded that further studies were necessary to evaluate HSO as a primary tamponade, particularly in simple primary inferior RRDs.[27]

The use of silicone oil, including Densiron, was at the discretion of individual surgeons and as such, varied. In our database, the proportion of RRD cases treated with any type of silicone oil varies 10-fold between surgeons, ranging from 2.5% to 25%, with a mean of 8.9%. Our analysis of unmatched data indicates a preference for using Densiron in eyes with predominantly inferior retinal breaks and LSO in eyes with mainly superior breaks (Tables S2 and S3, Fig S6, available at www.aaojournal.org). To address the risk associated with inferior retinal breaks, we matched on the basis of the location of the most inferior break, achieving excellent balance in both arms (88%; 125 of 142 Densiron, 250 of 284 LSO) below the 4−8 o'clock positions (Table S4 and Fig S6, available at www.aaojournal.org). Despite matching on inferior retinal pathology, our sample included eyes with the most superior break above the midline in both groups (Table S3, Fig S6, available at www.aaojournal.org). Notably, in our matched anatomic analysis, 44% (63 of 142) of Densiron-treated eyes and 68% (194 of 284) of LSO-treated eyes had breaks above the 2−10 o'clock positions, suggesting Densiron's efficacy extends to cases with superior breaks as well. Although the matched groups showed imbalances in other variables (Table 1), achieving perfect balance on all measures is not feasible with any matching strategy. Therefore, we controlled for these and other possible confounders by adjusting for them as covariates and treatment−covariate interactions in our analyses, including positions of the lowest, centermost, and highest retinal breaks.

Limitations

Our study has several limitations. First, our requirement that postoperative VA be measured at least 2 months after oil removal led to the inclusion of few eyes with anatomic failure in our matched sample for visual analyses. Therefore, the observed benefits of Densiron on postoperative VA over LSO may not be generalizable to populations with higher anatomic failure rates. We also used a strict definition of primary anatomic success, without data on final attachment, so it is possible that long-term results may be different from those presented. Additionally, both groups had a relatively low use of combined scleral buckles, although this was higher in the LSO group (3.5% or 2.8% vs. 0% in the matched anatomic and visual samples, respectively; Tables 1 and S2). It is possible that even greater use of scleral buckling in the LSO group could have improved the results in this arm. Although recent observational case series suggest benefits of this approach in preventing re-detachment,[28,29] especially in phakic eyes and those with inferior retinal breaks, systematic reviews have not confirmed this, and the available evidence remains of low certainty,[30−32] emphasizing the need for further studies. Furthermore, the database relies on sequential accurate data entry by users that has not been formally verified. Nevertheless, the frequency of oil use and baseline clinical characteristics in our study match those reported in a large, validated UK-based audit, suggesting that our data are representative.[33]

Last, our study was not designed to evaluate known Densiron complications such as inflammation, emulsification, and high intraocular pressure, but we expect any significant impact on clinical outcomes to have been reflected in our analyses. It is worth noting that Densiron Xtra was introduced at the beginning of our study period. Although our databases do not record the type of Densiron used, this substitution may have impacted the occurrence of emulsification-related complications.[21] Likewise, we could not analyze other heavier-than-water oil tamponades due to a lack of data, so it is unclear if our results would be comparable to other HSOs.

Conclusions

Our study suggests that surgeons should consider using Densiron tamponade for the treatment of primary RRD in eyes with predominantly inferior retinal pathology and PVR-C given its improved anatomic and visual outcomes relative to LSOs. We have demonstrated that the resulting effect estimates are unbiased and likely generalizable to other populations like ours. Further research is warranted to confirm the causal pathways between Densiron use and improved outcomes and to investigate potential adverse events associated with its use.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. As per UK guidance, data collection is classified as an audit for the purpose of service evaluation, so Institutional Review Board approval and informed consent are not required. However, we obtained approval from each participating Hospital Trust before data compilation and analysis, in line with national information governance procedures. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Tzoumas, Yorston, Laidlaw, Williamson, Steel

Data collection: Tzoumas, Yorston, Laidlaw, Williamson, Steel

Analysis and interpretation: Tzoumas, Yorston, Laidlaw, Williamson, Steel

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Overall responsibility: Tzoumas, Yorston, Laidlaw, Williamson, Steel

Abbreviations and Acronyms:

CI = confidence interval; **cSt** = centistokes; **Densiron** = Densiron 68; **HSO** = heavy silicone oil; **logMAR** = logarithm of the minimum angle of resolution; **LSO** = light silicone oil; **MD** = mean difference; **OR** = odds ratio; **PDMS** = polymerized siloxane (polydimethylsiloxane); **PVR** = proliferative vitreoretinopathy; **PVR-C** = proliferative vitreoretinopathy grade C; **RD** = retinal detachment; **RRD** = rhegmatogenous retinal detachment; **VA** = visual acuity; **VH** = vitreous hemorrhage.

Keywords:

Densiron, Retinal detachment, Silicone oil, Tamponade agent, Vitreoretinal surgery.

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