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Slow-Release Dexamethasone in Proliferative Vitreoretinopathy

A Prospective, Randomized Controlled Clinical Trial

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Purpose: To test the hypothesis that adjunctive slow-release dexamethasone implant (Ozurdex; Allergan Inc, Irvine, CA) can improve the outcomes of vitreoretinal surgery for established proliferative vitreoretinopathy (PVR).

Design: A 2-year, single-center, prospective, participant- and surgeon-masked randomized controlled clinical trial (EudraCT No. 2011-004498-96).

Participants: A total of 140 patients requiring vitrectomy surgery with silicone oil for retinal detachment with established PVR (Grade C) were randomized to standard (control) or study treatment (adjunct) in a 1:1 allocation ratio.

Methods: Intraoperatively, the adjunct group received an injection of 0.7 mg of slow-release dexamethasone (Ozurdex) at the time of (1) vitrectomy surgery and (2) silicone oil removal. The control group received standard care.

Main Outcome Measures: Primary outcome measure was the proportion of patients with a stable retinal reattachment with removal of silicone oil without additional vitreoretinal surgical intervention at 6 months. Secondary outcomes included (1) final visual acuity (VA) (median and Early Treatment Diabetic Retinopathy Study [ETDRS] of 55 letters or better); (2) cystoid macular edema (CMO), foveal thickness, and macular volume; (3) development of overt PVR recurrence; (4) complete and posterior retinal reattachment; (5) tractional retinal detachment; (6) hypotony/increased intraocular pressure (IOP); (7) macula pucker/epiretinal membrane; (8) cataract; and (9) quality of life.

Results: All 140 patients were recruited within 25 months of study commencement; 138 patients had primary outcome data. Primary outcome assessment showed similar results in anatomic success between the 2 groups (49.3% vs. 46.3%, adjunct vs. control; odds ratio, 0.89; 95% confidence interval, 0.46−1.74; $P = 0.733$). Mean VA at 6 months was 38.3 ETDRS letters and 40.2 letters in the adjunct and control groups, respectively. Secondary anatomic outcomes (complete/posterior reattachment rates and PVR recurrence) were comparable between the 2 groups. At 6 months, fewer adjunct patients had CMO (42.7%) or a foveal thickness of >300 μm (47.6%) compared with controls (67.2% and 67.7%, respectively, $P = 0.004$, $P = 0.023$).

Conclusions: A slow-release dexamethasone implant did not improve the primary anatomic success rate in eyes undergoing vitrectomy surgery with silicone oil for PVR. Further clinical trials are indicated to improve anatomic and visual outcomes in these eyes, but this study suggests that there is a greater reduction in CMO observed at 6 months in vitrectomized eyes treated with slow-release dexamethasone. *Ophthalmology 2017;124:757-767 © 2017 by the American Academy of Ophthalmology*

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Proliferative vitreoretinopathy (PVR) is the most common cause of late anatomic failure after vitrectomy for rhegmatogenous retinal detachment. Its reported incidence ranges from 5% to 11% of all rhegmatogenous retinal detachments.[1] Proliferative vitreoretinopathy can be considered a maladapted wound-healing retinal response in which cellular proliferation, migration, and deposition result in the formation of fibrocellular membranes on both surfaces of the retina and the posterior hyaloid face.[1] Contraction of these membranes can result in distortion of normal retinal topography with visually detrimental sequelae or tractional retinal detachment, with the reopening of preexisting breaks or the formation of new breaks.

Proliferative vitreoretinopathy is a challenging vitreoretinal surgical problem, and despite improvements in instrumentation and technique, a significant number of cases fail to achieve reattachment. Multiple procedures are frequently required to eventually achieve final retinal attachment with poor visual results and unsatisfactory

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binocular visual outcomes.[1–3] Furthermore, PVR management is costly in patient time and healthcare resources.[3] Numerous adjunctive medications have been evaluated in clinical trials,[4–12] yet no effective and safe adjunct has gained widespread acceptance.

Experimentally, corticosteroids potentially can influence both the inflammatory and the proliferative components of the PVR process via a variety of modes of administration[13–15] without evidence of demonstrable retinal toxicity.[16]

Clinically, intravitreal crystalline cortisone was first reported in 2000 by Jonas et al[17] to be well tolerated in PVR cases undergoing vitrectomy. Previous small-scale, uncontrolled clinical studies of PVR have suggested that systemic prednisolone,[18] infused dexamethasone,[19] and intravitreal triamcinolone[20,21] may reduce the severity of PVR, although none of these studies were of sufficient power to provide a definitive answer. A slow-release preparation of corticosteroid may offer additional advantages over other agents, through sustained activity during the active phase of the PVR process.

The aim of this study was to determine whether a 0.7 mg slow-release preparation of dexamethasone given at the time of vitrectomy surgery and repeated at the time of oil removal could improve anatomic and visual outcomes at 6 months after surgery in eyes with PVR.

Methods

This phase IIIb, single-center, participant-masked, prospective, randomized controlled clinical trial was performed at Moorfields Eye Hospital NHS Foundation Trust between February 2012 and February 2015.[22] Before participant recruitment, Moorfields Research Management Committee approval was obtained, a favorable opinion from the National Research and Ethics Service Committee London—Central was received (11/LO/1685), and the study was granted a clinical trials authorization by the Medicines and Healthcare Products Regulatory Agency. The trial was registered on the European Clinical Trials Database (EudraCT No 2011-004498-96). The study was conducted in accordance with the International Conference on Harmonisation for Good Clinical Practice, as set out in the European Union Clinical Trials Directive (2001) and associated UK Regulations (2004). The study complied at all times with the Declaration of Helsinki (2000). Patients provided written informed consent before entering the trial. An independent Data Monitoring Committee (DMC) and Trial Steering Committee provided study oversight throughout the duration of the trial.

Participants

The study population consisted of male and female patients 18 years of age and older. Eligible patients were those undergoing pars plana vitrectomy with silicone oil tamponade for rhegmatogenous retinal detachment with established (Grade C) PVR.[23]

The exclusion criteria were as follows: (1) open globe injury; (2) a diagnosis of ocular hypertension on 2 or more pressure-lowering medications or a definite diagnosis of glaucoma (if in the opinion of a glaucoma specialist, the patient is at high risk of visual damage from increased intraocular pressure [IOP]); (3) uncontrolled uveitis; (4) previous steroid-induced glaucoma; (5) proliferative diabetic retinopathy or vasculopathy; (6) pregnant or breastfeeding females; (7) previous known adverse reaction to Ozurdex (Allergan Inc, Irvine, CA); (8) suspected ocular/periocular infection (e.g., herpes simples virus, varicella zoster virus, mycobacterial infection, fungal disease); (9) aphakia or patients in whom a lensectomy is planned at time of surgery; and (10) preexisting anterior chamber intraocular lens. There were no restrictions on the number of previous vitreoretinal procedures.

Randomization

A randomization schedule of 140 treatment allocations against 140 study identifiers was produced by the senior data manager using random permuted blocks of varying sizes. The randomization schedule was provided to the clinical trials pharmacy at the study site, who prepared treatment packs according to the randomization schedule. On confirmation of eligibility, participants were allocated to the lowest unused study number. Out of hours (i.e., weekends and bank holidays), the next study number in sequence was kept in a sealed treatment pack in a secure location on site when access to the trials pharmacist was limited. Seventy patients were randomized to receive standard surgical care (control group), and 70 patients were randomized to receive standard surgical care in addition to the supplementary adjunctive dexamethasone implant (adjunct group).

Intervention

Both groups received the standard vitreoretinal operative procedure that their ocular condition required. Consultants or senior fellows (second-year fellowship) performed the operative procedures.

Adjunct Group

On confirmation of successful retinal reattachment and completion of silicone oil exchange, the operating surgeon was asked to clinically grade the level of PVR using the standardized classification system in current practice.[23] Thereafter, the surgeon was asked to inject a 0.7-mg slow-release dexamethasone implant through the final open sclerotomy port before suturing.

A similar procedure was followed for the second implant administration at the time of oil removal. On confirmation that the retina remained attached after removal of oil, the surgeon was again asked to confirm the retinal status and the presence or absence of PVR. Because a variety of techniques were used to remove silicone oil, particularly if combined cataract surgery was performed, the implant was injected through a sclerotomy port (if used) or via the conventional method of delivery.[24]

Control Group

After successful retinal reattachment, completion of silicone oil exchange, and grading the level of PVR, the surgeon was informed that no adjunctive medication was required and the final sclerotomy port was sutured.

Masking

Participants were masked to their treatment allocation for their entire duration of the trial, and preservation of masking status was confirmed on exit. In addition, the operating surgeon was masked until the end of the surgical procedure to avoid any bias in surgical management. The treatment allocation was revealed to the operating surgeon in a manner by which the patient remained masked. It was not possible to mask the investigators at follow-up, because the primary investigational medicinal product (IMP) was sometimes visible on posterior chamber assessment.

Assessments and Schedule

Postoperative study visits mirrored the routine schedule for vitreoretinal procedures at the study site and were conducted in the National Institute for Health Research Clinical Research Facility at Moorfields Eye Hospital (P.J.B., T.M.Z., D.G.C.) at day 1, day 10, 4 to 6 weeks, 3 months, 6 months, 9 months, and 12 months. At each scheduled postoperative study visit, a full ophthalmic assessment was completed to include slit-lamp biomicroscopy (± indirect binocular ophthalmoscopy when required) to assess retinal attachment status and PVR grade,[23] and parameters including best-corrected visual acuity (VA) (ETDRS chart) applanation tonometry and anterior segment assessment were recorded. Spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany) was used to determine the presence or absence of cystoid macular edema, epiretinal membrane, and persistent submacular fluid. Central foveal thickness and macular volume were determined using automated algorithms incorporated into the Heidelberg software.

Where indicated, silicone oil removal was routinely performed 4 months after the study vitrectomy to allow sufficient time to adequately test the primary outcome measure at month 6.

Two additional study visits at day 60 after implant injection were performed to measure the IOP. Management of postoperative elevated IOP followed an algorithm previously approved by an independent glaucoma specialist who was a member of the external DMC.[22]

Any additional vitreoretinal surgical interventions over the trial period were considered reoperations and recorded as such. Indirect laser retinopexy was performed at the discretion of the patient's vitreoretinal consultant and was not considered a reoperation.

Adverse Events

Adverse events were recorded and reported to the sponsor as per the study protocol.[22] Study-specific definitions for elevated IOP (>25 mmHg) were adhered to. Furthermore, because cataract is an inevitable consequence of vitrectomy surgery, it was only considered an adverse event (AE) if in the treating clinician's opinion it had progressed at a rate requiring expedited surgical extraction before the planned removal of silicone oil.

Primary Outcome

The primary outcome measure was the proportion of patients with a stable retinal reattachment with removal of silicone oil without additional vitreoretinal surgical intervention at 6 months after study vitrectomy.

Secondary Outcomes

Secondary outcomes at 6 and 12 months after primary study vitrectomy surgery were as follows:

1. VA (a comparison of the mean/median VA and the proportion of patients in each group achieving a VA of 55 ETDRS letters or better);
2. Macula edema and thickness (OCT analysis), that is, the proportion of patients in each group with a central A1 macula subfield measure of >300 μm;
3. The proportion of patients in each group who develop overt PVR recurrence;
4. The proportion of patients in each group achieving complete retinal reattachment;
5. The proportion of patients in each group achieving stable posterior (post equatorial) retinal reattachment;
6. The proportion of patients in each group with a tractional retinal detachment;
7. The proportion of patients in each group who have hypotony (defined as IOP <6 mmHg) or increased IOP (defined as >25 mmHg) at any time point during the study period;
8. The proportion of patients in each group who develop the presence of macula pucker/epiretinal membrane and/or require macula epiretinal membrane surgery at any time point during the study;
9. The proportion of patients in each group who require cataract surgery at any time point during the study; and
10. Quality of life assessment—a comparison in the median/mean scores of both Social Functioning 36-point Questionnaire and Visual Functioning 25-point Questionnaire between both groups.

Sample Size

On the basis of the results of the primary outcome measure from a trial of the same patient group carried out in the study center,[7] 66 patients per study arm are required for a study power of 85% to detect, at the 5% level, a 50% improvement in success of the adjunctive regimen (reducing failure from 49% to 24%). This reduction in failure rate was deemed clinically meaningful and of sufficient magnitude to change clinical practice. Allowing for a 5% loss to follow-up rate (observed in previous studies at the study site[6–8]), a total sample size of 140 patients is necessary.[25]

Statistical Analysis

Baseline characteristics for each group were presented as mean and standard deviation (SD) for continuous (approximately) normally distributed variables, medians and interquartile ranges (IQR) for non-normally distributed variables, and frequencies and percentages for categoric variables.

Analysis was conducted following the intention-to-treat principle. An available case analysis was conducted together with best/worst case scenario imputation analysis, and results were compared in a sensitivity analysis. For the primary outcome, reasons for missingness were examined using logistic regression of covariates on an indicator of missingness. All statistical tests used a 2-sided P value of 0.05. All confidence intervals (CIs) presented were 95% and 2 sided.

The primary outcome was reported by treatment group with 95% CIs computed by the exact binomial method. Treatment effect estimate was computed as an odds ratio (OR) and respective 95% CI using univariate logistic regression. Treatment effect estimates with 95% CIs also were computed by PVR severity (severe, anterior grade, or posterior grade C >4 vs. less severe, anterior grade and posterior grade C ≤4).

Summary statistics for all secondary outcomes were computed by treatment group at 6 and 12 months after initial surgery (12 months data to be disseminated separately). Analysis of covariance was used to explore the difference between treatment arms in change from baseline in continuous variables (e.g., VA, quality of life).

Sensitivity analysis was conducted using analysis of covariance to explore difference between treatment arms in change from baseline in VA at 6 and 12 months for the subgroup of patients with no prior reason for poor visual outcome (12 months data to be disseminated separately). This subgroup of patients was identified by the clinician (P.J.B.) masked to treatment allocation and outcome. The proportion of patients who experience an AE or a serious AE was reported by event type and treatment group.

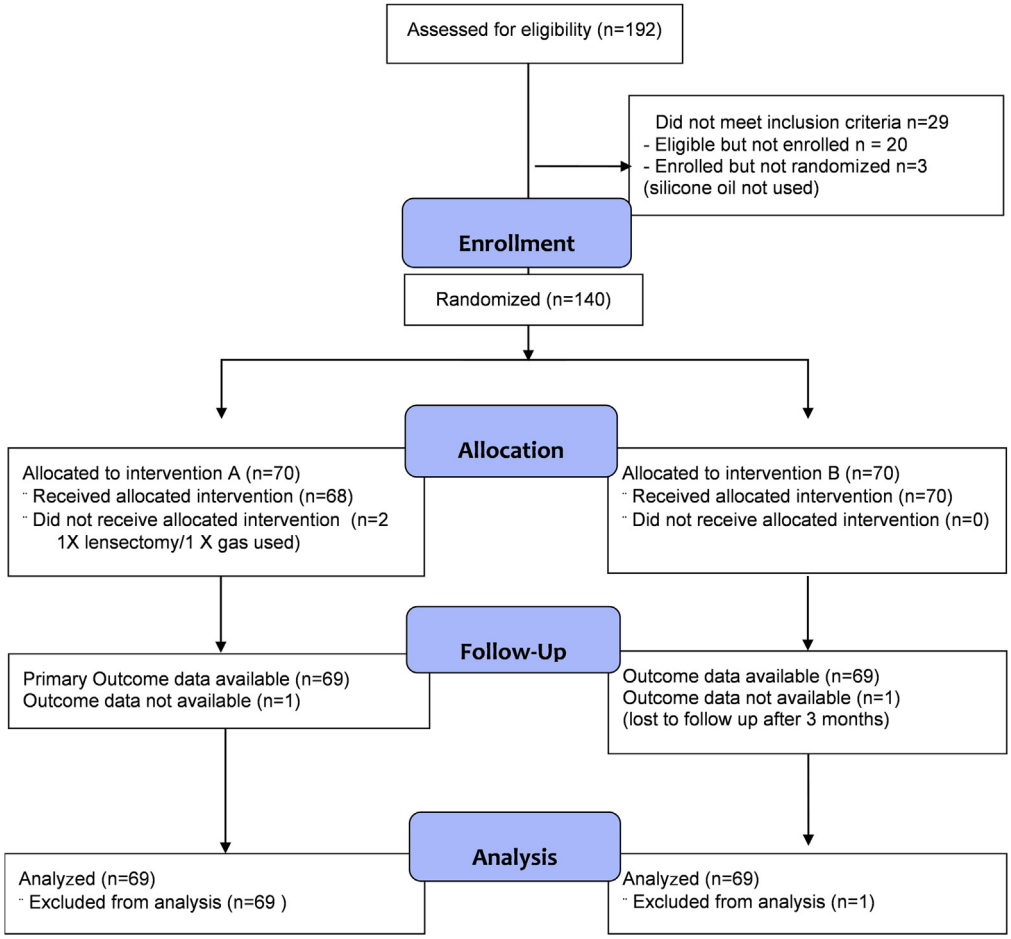

Figure 1. Ozurdex (Allergan Inc, Irvine, CA) in proliferative vitreoretinopathy (PVR) consort diagram. A total of 140 of 163 eligible patients were recruited within 24.5 months of the study commencing. Primary outcome data were available and analyzed for 69 of 70 patients in each group.

A post hoc exploratory analysis was conducted on patients with available quantitative SD OCT readings at 6 months, using chi-square tests to compare the proportion of patients with cystoid macular edema (CMO) by treatment arm and the proportion of patients with a foveal thickness greater than 300 μm by treatment arm.

Results

Figure 1 displays the consort flow diagram. Patient recruitment opened in February 2012. A total of 192 patients were assessed for eligibility, of whom 29 were ineligible and excluded. Of the remaining 163 eligible patients, 20 declined to participate in the study. Three further patients enrolled in the study but were not randomized because silicone oil was not used. The remaining 140 eligible patients elected to participate in the trial and were recruited within 24.5 months of the study commencing. The study closed at the final visit of the final patient in February 2015 within the original projected timeframe.

Baseline Characteristics

Baseline demographic and nonocular characteristics are summarized in Table 1 showing comparable gender, mean age, and ethnicity, with a white sexagenarian male preponderance in both groups. Ocular and retinal baseline characteristics are displayed in Tables 2A, 2B, and 3.

The median refractive status in both groups was emmetropia. Approximately one-third of eyes in each group (n = 22 vs. n = 20, adjunct vs. control, respectively) had not undergone previous vitreoretinal surgery, with the majority of the remaining two-thirds of patients undergoing failed vitrectomy surgery with gas tamponade. Four patients in both groups had previously undergone failed scleral buckling procedures. Twice as many patients in the adjunct group (n = 20) were noted to have ocular comorbidity compared with the control group (n = 10). These included a history of amblyopia, age-related macular degenerative disease, and closed globe ocular trauma.

The median presenting VA was zero ETDRS letters (i.e., counting fingers or less) in both groups (IQR, 0–22 adjunct, 0–31 control), and mean IOP readings were 11.9 mmHg (SD, 4.9) and 13.3 mmHg (SD, 5.1) in the adjunct and control groups, respectively. Baseline markers of inflammation and blood ocular barrier breakdown (anterior chamber cells, vitreous hemorrhage, and RPE cells) were comparable between the 2 groups.

Thirty-seven (52.9%) of the adjunct group patients were pseudophakic compared with 34 (48.6%) control patients. Of the remainder, the majority showed signs of lens opacity, with approximately 10% of patients in each group with no cataract.

The fovea was detached in 60 of 70 eyes (85.7%) in the adjunct group and in 57 eyes (81.4%) in the control group. The median

Table 1. Nonocular Baseline Characteristics

	Adjunct Group (N = 70)	Control Group (N = 70)
No. of patients (eyes), n (%)	70 (70)	70 (70)
Male/female, n (%)	46 (65.7)/24 (34.3)	40 (57)/30 (43)
Age in yrs, mean (SD)	60.6 (14.3)	61.6 (13.9)
Ethnicity, n (%)		
White	53 (75.7)	57 (81.4)
Black	6 (8.6)	4 (5.7)
Asian	10 (14.3)	6 (8.6)
Other	1 (1.4)	3 (4.3)
Scores		
VFQ-25, median (IQR)	66 (50–77)	65 (55–76)
Missing, n (%)	1 (1.4)	3 (4.3)
SF-36, median (IQR)	63 (45–75)	72 (52–84)
Missing, n (%)	1 (1.4)	3 (4.3)

IQR = interquartile range; SD = standard deviation; SF-36 = Social Functioning 36-point Questionnaire; VFQ-25 = Visual Functioning 25-point Questionnaire.

duration of retinal detachment was 25 (IQR, 14–52) and 21 (IQR, 10–35) days in the adjunct and control groups, respectively. The median extent of retinal detachment was comparable, with 8 clock hours of RD recorded in the adjunct group and 9 clock hours in the control arm. The median grades of anterior and posterior PVR (as assessed intraoperatively) were comparable between the 2 groups.

Operative Techniques

Table 4 outlines the operative techniques used during the primary study vitrectomy. A total of 38 adjunct patients (54.3%) and 39 control patients (55.7%) underwent a retinectomy at the time of their primary study vitrectomy. Comparable numbers of patients in each group underwent indirect laser retinopexy before oil removal (14 control patients and 15 adjunct patients).

Table 2A. Baseline Ocular Characteristics (Nonretinal)

	Adjunct Group (N = 70)	Control Group (N = 70)
Laterality (left eye), n (%)	36 (51.4)	38 (54.3)
Refraction (SE) median (IQR)	−0.6 (−5 to 0)	0 (−2.63 to 0)
Missing, n (%)	9 (12.9)	13 (18.6)
Previous VR surgery, n (%)		
None	22 (31.4)	20 (28.6)
V/gas	36 (51.4)	36 (51.4)
V/oil	11 (15.7)	11 (15.7)
V/B	0	1 (1.4)
C/B	4 (5.7)	4 (5.7)
Mac-off episodes, median (IQR)	2 (1, 2)	2 (1, 2)
Coexisting ocular pathology, n (%)		
Macular pathology	3 (4.3)	2 (2.9)
Amblyopia	5 (7.1)	0
Corneal scar	0	1
Other	2 (2.9)	0

C/B = cryotherapy/buckle; IQR = interquartile range; mac off episodes = known episodes of fovea-involving retinal detachments; SE = spherical equivalent; V/B = vitrectomy/buckle; V/gas = vitrectomy/gas; V/oil = vitrectomy/oil; VR = vitreoretinal.

Table 2B. Baseline Ocular Characteristics (Nonretinal)

	Adjunct Group (N = 70)	Control Group (N = 70)
ETDRS VA, median (IQR)	0 (0–22)	0 (0–31)
IOP, mean (SD)	11.9 (4.9)	13.3 (5.1)
AC inflammation (cell count), n (%)*		
None (0)	38 (54.3)	33 (47.1)
Mild (1+)	30 (42.9)	29 (41.4)
Moderate (2+)	1 (1.4)	8 (11.4)
Severe (3+, 4+)	1 (1.4)	0
Lens status, n (%)		
Clear	8 (11.4)	7 (10)
PCIOL	37 (52.9)	34 (48.6)
Cataract	25 (35.7)	29 (41.4)
Vitreous hemorrhage, n (%)		
Absent	66 (94.3)	67 (95.7)
Present	4 (5.7)	3 (4.3)

AC = anterior chamber; ACIOL = anterior chamber intraocular lens; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; IQR = interquartile range; PCIOL = posterior chamber intraocular lens; SD = standard deviation; VA = visual acuity.
*AC inflammation cell count according to Standardization of Uveitis Nomenclature classification.

Primary Outcome Measure

Primary outcome data were available for 69 of 70 patients in each group. One patient in the control group was lost to follow-up after month 3, and 1 patient in the adjunct group was prematurely withdrawn because the patient had failed primary surgery and no month 6 data were collected. It was subsequently agreed by both the Trial Steering Committee and DMC that this adjunct patient should remain in the study, and month 12 data were collected.

There was no observed difference in primary outcome between the 2 groups (Table 5); 49% of patients (n = 34 of 69) in the adjunct group achieved a stable retinal reattachment with silicone

Table 3. Baseline Retinal Status

	Treatment Group (N = 70)	Control Group (N = 70)
Summed duration of RD, median (IQR)	28 (7–45)	25 (11–52)
Not possible, n (%)	17 (24)	21 (30)
Clock hours of RD primary/baseline, median (IQR)	6 (5–10)/8 (6–11)	6.5 (5–11)/9 (6–12)
Not possible, n (%)	7 (10)/24 (34)	8 (11)/24 (34)
Macular status, n (%)		
Attached	10 (14.3)	13 (18.6)
Detached	60 (85.7)	56 (80)
Bisected	0	1 (1.4)
PVR grade,* median (IQR)		
CP	3 (2–4)	4 (2–6)
CA	4 (3–6)	4 (4–6)

CA = anterior grade; CP = posterior grade C; IQR = interquartile range; PVR = proliferative vitreoretinopathy; RD = retinal detachment.
*Measured at operation.

Table 4. Operative Techniques during Study Vitrectomy

	Adjunct Group (n = 70)	Control Group (N = 70)
Lensectomy, n (%)	1	1
PVD induction, n (%)	5	4
PFCL, n (%)	40 (57)	44 (63)
Retinectomy, n (%)	38 (54)	39 (56)
PVR membrane peel, n (%)	42 (60)	38 (54)
Segmental buckle, n (%)	1	2
Retinopexy, n (%)		
Endolaser	56 (80)	58 (83)
Cryotherapy	43 (61)	48 (69)

PFCL = perfluorocarbon; PVD = posterior vitreous detachment; PVR = proliferative vitreoretinopathy.

oil removal without additional vitreoretinal surgical intervention at 6 months, compared with 46% (n = 32 of 69) in the control group (OR, 0.89; 95% CI, 0.46−1.74; $P = 0.733$ chi-square). Best-case and worst-case imputation analysis did not affect the primary outcome findings. Subgroup analysis stratifying by severity of PVR (posterior grade C or anterior grade >4) did not show any statistically significant difference in primary outcome achievement.

Secondary Outcome Measures

Secondary outcome measures were assessed at 6 and 12 months after study vitrectomy. Six-month outcome measures are included in this report (Tables 6−8) and are reported on 138 of 140 patients unless otherwise stated in Tables 6-8. Twelve-month secondary outcome measures will be described in subsequent reports.

Visual Acuity

At 6 months after study vitrectomy, mean VA was comparable between the 2 treatments: 38.3 ETDRS letters (SD, 23.7) in the adjunct group compared with 40.2 letters (SD, 21.1) in the control group (Table 6). A sensitivity analysis excluding eyes with preexisting ocular comorbidity limiting visual outcome was performed and did not affect the findings. The proportion of eyes achieving a VA ≥55 ETDRS letters also was comparable, with 21 of 69 eyes (30%) in the adjunct group achieving this vision or better, compared with 17 of 69 eyes (24%) in the control group.

Secondary Anatomic Outcomes

At 6 months, the proportion of patients achieving complete retinal reattachment or a stable posterior retinal reattachment was comparable between the 2 treatment groups (Table 7). Likewise, the proportion of patients with a tractional retinal detachment at 6 months was comparable. The rate of overt PVR recurrence (defined as the presence of postoperative PVR at any time point up to 6 months after study vitrectomy) was 57.0% (n = 40) in the adjunct group and 59% (n = 41) in the control group.

There was no observed difference in the number of operations to achieve primary success (as defined in the primary outcome measure); however, 11 patients (16%) underwent more than 1 operation to achieve success in the control group compared with 3 patients (4.4%) in the adjunct group.

Macular Findings

At 6 months, for patients with available quantitative SD OCT readings, median foveal thickness and macular volume were lower in the adjunct group (297 μm and 8.85 mm^3, respectively) compared with the control group (365 μm and 9.23 mm^3, respectively). Likewise, the proportion of eyes with a foveal thickness >300 μm in the A1 macular subfield was lower in the adjunct group (n = 30, 47.6%) compared with the control group (n = 42, 67.7%) (OR, 2.3; 95% CI, 1.12−4.78; $P = 0.023$, chi-square). Furthermore, the proportion of eyes with macular edema in the adjunct group was 42.7% (n = 29) compared with 67.2% (n = 45) (OR, 2.8, 95% CI, 1.37−5.54; $P = 0.004$, chi-square). Forty patients (57.1%) in the adjunct group and 41 patients (58.6%) in the control group developed macular epiretinal membrane at any time point up to 6 months, with comparable rates of macular pucker surgery between the 2 groups (Table 8).

Cataract and Intraocular Pressure Outcomes

The proportion of phakic patients in the adjunct group who underwent cataract surgery in the 6 months after the study intervention was 75.8% (n = 25 of 33), compared with 86.1% in the control group (n = 31 of 36). At 6 months, 84.1% of adjunct patients (n = 58) were pseudophakic compared with 87% of control patients (n = 60).

Rates of hypotony were similar between the 2 groups, with 20% of patients (n = 14) in the adjunct group having least 1 episode of hypotony and 24.3% (n = 17) of patients in the control group having least 1 episode of hypotony. The median and IQR IOP per time point by treatment group is displayed in the boxplot in Figure 2. More patients in the adjunct group (n = 32, 45.7%) experienced at least 1 episode of elevated IOP compared with the control group (n = 22, 31.4%).

Quality of Life Parameters

Mean Social Functioning 36-point Questionnaire and Visual Functioning 25-point Questionnaire scores and mean change from baseline showed no evidence of a difference between the 2 treatment groups (Table S1, available at www.aaojournal.org).

Adverse Events and Serious Adverse Events

There were no serious adverse reactions observed in either group. The AEs are displayed in Table S2 (available at www.aaojournal.org) and totaled 595 episodes, with 285 events in the adjunct group compared with 310 in the control group. A total of 66 of 70 (94.3%) adjunct patients had at least 1 AE compared with 63 of 70 control patients (90.0%).

Table 5. Primary Outcome Result (Available Intention-to-Treat Analysis)

	Adjunct Group (N = 69)	Control Group (N = 69)	Effect Estimate OR (95% CI)
Proportion of patients satisfying primary outcome measure, % (95% CI)	49 (37−62)	46 (34−59)	0.89 (0.46−1.74)

CI = confidence interval; OR = odds ratio.

Table 6. Secondary Outcome Measures: Visual Acuity at 6 Months

	Adjunct Group (N = 69)	Control Group (N = 69)	Effect Estimate (95% CI)
ETDRS BCVA, mean (SD)			
At 6 mos	38.3 (23.7)	40.2 (21.1)	-
Change from baseline at 6 mos*	24.5 (28.6)	23.1 (26)	1.1 (−6.3 to 8.4)
Proportion of patients achieving ETDRS VA ≥55, n (%)	21 (30)	17 (24)	-
Sensitivity analysis	(N = 59)	(N = 66)	
ETDRS BCVA, mean (SD)			
At 6 mos	41.60 (23.1)	41 (20.9)	-
Change from baseline at 6 mos*	26.4 (29.3)	23.2 (26.4)	−1.2 (−8.8 to 6.4)

BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation; VA = visual acuity.
*Adjusted for respective baseline.

The most common AE was elevated IOP. In the adjunct group, there were 85 episodes (39.2%) of increased IOP compared with 75 (31.4%) in the control group. There were 17 serious AEs during the study (16 nonocular and 1 ocular), which were comparably distributed between the 2 groups (Table S3, available at www.aaojournal.org). The ocular serious AE was a corneal suture-related abscess necessitating a hospital admission at the patient's local hospital. This was deemed unrelated to the IMP and recorded as such. There were more cases of postoperative uveitis in the control group (n = 24) in comparison with the adjunct group (n = 10).

Discussion

Dexamethasone has a potency that is 5 times greater than triamcinolone,[26] and being more hydrophilic, allows for higher vitreous concentrations.[27] However, its clinical utility had previously been limited by its short half-life[28] and therefore necessitated the development of a slow-release drug-delivery system.

The slow-release dexamethasone preparation (Ozurdex), is a 6-mm implant containing 700 μg of dexamethasone in a biodegradable polymer (Novadur, Allergan, Irvine, CA). It exhibits a dual-phase response of initially high concentrations of dexamethasone in the first 2 months, followed by a period of lower concentrations sustained for up to 6 months postinjection.[29] In experimental studies, its pharmacokinetic profile was unaffected in vitrectomized eyes.[30] In 2011, it was first licensed for use in the treatment of macular edema secondary to retinal vein occlusion[31] and noninfectious posterior uveitis.[32] Its market authorization was subsequently expanded in 2014 to include patients with diabetic macular edema.[33]

Table 7. Secondary Outcome Measures: Anatomic Findings at 6 Months

	Adjunct Group (N = 69)	Control Group (N = 69)
Overt PVR recurrence* n (%)	40 (57)	41 (59)
Complete retinal reattachment† n (%)	37 (53.6)	43 (62.3)
Stable posterior retinal reattachment† n (%)	46 (66.7)	48 (69.6)
TRD† n (%)	15 (22)	13 (19)
No. of procedures to achieve attachment, n (%)		
0	41 (59.4)	37 (53.6)
1	25 (36.2)	21 (30.4)
2	3 (4.4)	11 (16)

PVR = proliferative vitreoretinopathy; TRD = tractional retinal detachment.
*Between the primary study vitrectomy and 6 months.
†Without silicone oil in situ.

This is the first published randomized controlled clinical trial investigating the use of a slow-release preparation of corticosteroid in PVR. Recruitment was completed within the projected timescale, and study retention rate was favorable at 98.6%. To date, there have been 8 randomized controlled clinical trials[4,6–8,10,34–36] investigating a variety of pharmacologic adjuncts targeting varying components of the PVR process. As yet, no single agent or combination has gained widespread acceptance.

We found no difference in the proportion of patients achieving stable retinal reattachment with silicone oil removal without additional vitreoretinal surgical intervention at 6 months. Approximately one-half of patients achieved primary success in both groups (49.3% vs. 43.3%, adjunct vs. control), which is similar to previously published rates in randomized controlled clinical trials adopting a comparable primary outcome measure.[7,36] In a study comparing the effect of 4 mg of intravitreal triamcinolone, Ahmadieh et al[34] published an overall primary success rate of 81.3% in eyes with Grade C PVR undergoing vitrectomy surgery with an encircling scleral buckle. They observed no difference in primary or secondary outcomes between the adjunct and control arms.

Although the proportion of patients in our trial achieving the primary outcome measure in each treatment group was similar, our study was powered to detect a 50% reduction in failure rate. It is possible that a larger trial powered to detect a smaller difference (i.e., ≤25%) might determine a positive treatment effect on anatomic success rates. However, because the sample size would inevitably be larger, it is likely that a multicenter approach would need to be adopted.

If we consider secondary outcomes indicative of the effect of the IMP on the PVR process, we found only limited

Table 8. Secondary Outcome Measures: Macular Findings at 6 Months

	Adjunct Group (N = 69)	Control Group (N = 69)	Effect Estimate (95% CI, P Value)
CMO present, n (%)*	29 (42.7)	45 (67.2)	2.8 (1.37–5.54, P = 0.004)
FT >300 μm, n (%)‡	30 (47.6)	42 (67.7)	2.3 (1.12–4.78, P = 0.023)
FT, median (IQR)	297 (255–380)	365 (284–455)	–
Missing, n (%)	6 (9)	7 (10)	
Macular volume, median (IQR)	8.85 (8.32–9.77)	9.23 (8.18–10.36)	–
Missing, n (%)	6 (9)	8 (11)	
Macula pucker/ERM† n (%)	40 (57)	41 (58.6)	–
ERM surgery† n (%)	33 (47)	31 (44.3)	–

CI = confidence interval; CMO = cystoid macular edema; ERM = epiretinal membrane; FT = foveal thickness; IQR = interquartile range.
*Percentage expressed as proportion of available cases (68 eyes in adjunct group 67 eyes control group).
†Percentage expressed as proportion of n = 70.
‡Percentage expressed as proportion of available cases (63 eyes adjunct group, 62 eyes control).

evidence of differences between the 2 groups. A comparable proportion of patients achieved complete or posterior retinal reattachment and the proportion of eyes with a tractional RD or macular pucker was similar between the 2 study groups. Furthermore, rates of overt PVR recurrence were similar across both groups (57% vs. 59.4%, adjunct vs. control). We did note that fewer patients in the adjunct group (n = 3) required 2 or more operations to achieve attachment compared with the control group (n = 11). However, because this was not investigated as a secondary outcome and numbers are small, we did not test for statistical significance, and caution must be advised when interpreting this finding.

Despite finding no difference between retinal reattachment rates and PVR recurrence, statistically significantly fewer patients with quantitative SD OCT readings were noted to have cystoid macular edema at 6 months in the adjunct group (42.7%, n = 29) compared with 67.2% (n = 45) in the control group. Likewise, the proportion of eyes with a central foveal thickness of >300 μm in the A1 subfield was statistically significantly lower in the adjunct group (47.6%) in comparison with controls (67.7%). These statistical comparisons were conducted in a post hoc analysis and thus must be reported as exploratory. Although CMO and foveal thickness are related variables, additional factors such as epiretinal membrane may affect foveal

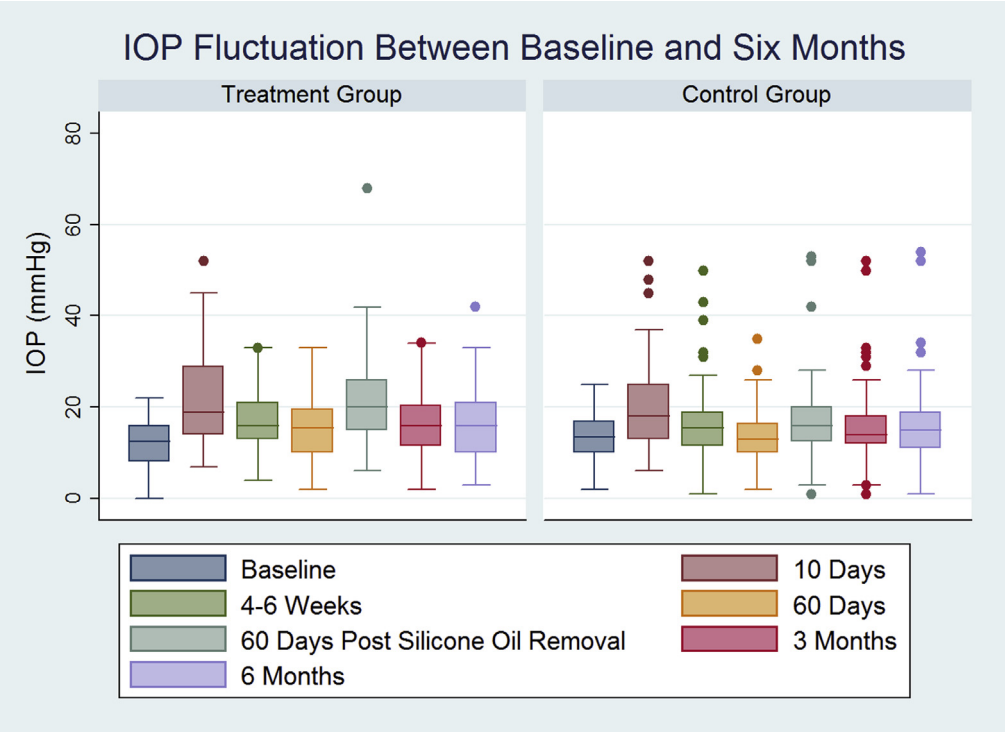

Figure 2. Boxplot of intraocular pressure (IOP) variation from baseline to month 6. Median IOP (*thick inner bar*) was comparable at all time points between both groups. *Box* denotes interquartile range (IQR), and *whiskers* indicate range excluding dot outliers.

thickness. Our findings are consistent with previous reports that a slow-release dexamethasone implant may be an effective treatment for CMO in vitrectomized eyes. Boyer et al[37] reported a statistically significant reduction in diabetic macular edema with corresponding visual improvement up to 6 months after implant injection in 55 vitrectomized eyes. Furthermore, other authors have reported that the same slow-release preparation has successfully treated refractory macular edema secondary to uveitis and venous occlusions, and after vitrectomy for retained lens fragments.[38–40]

Despite observing a difference in rates of postoperative CMO, we did not observe any difference in VA at 6 months. The mean VA in the adjunct group was 38.3 ETDRS letters (SD, 23.7) compared with 40.2 letters (SD, 21.1) in the control group. This equates to logarithm of the minimum angle of resolution (logMAR) VAs of 0.96 and 0.90, and approximates to a Snellen VA of 20/160. Likewise, the proportion of eyes achieving a VA $\geq$55 ETDRS letters ($>$20/80) was comparable (30.4% vs. 24.6%, adjunct vs. control). Mean final postoperative VA in eyes with PVR is notably poor, and reported levels range from 2.69 logMAR (light perception)[36] to 1.4 logMAR.[7,34] Our visual outcomes compare favorably to previous reports; however, a study investigating poor visual outcomes ($<$20/40) after successful RD repair for PVR in 35 patients reported a 66% incidence of CMO.[41] Given the lower incidence of macular edema observed in the adjunct group, one might have expected a correspondingly better visual outcome, especially when excluding eyes with limited visual potential. This observation is potentially important suggesting that retinal pathology other than macular edema such as neural retinal remodeling[42] may be the primary cause of the poor visual outcomes seen in PVR. Further studies are required to identify the cause of visual loss after RD surgery in eyes with PVR. The SD OCT imaging of eyes after fovea-involving RDs (without PVR) has correlated outer retinal abnormalities with poorer visual outcomes,[43–46] and thus may serve as a target for investigation in future studies.

Furthermore, replacing anatomic primary outcomes with a visual outcome seems to be a plausible design for future vitreoretinal clinical trials and is strongly advocated by patient groups involved in protocol development.[12,47,48]

Overall, we observed a higher number of AEs in the control group. There were fewer cases of postoperative uveitis in the adjunct group, perhaps indicative of the additional anti-inflammatory activity of the dexamethasone. There were more episodes and a greater proportion of patients experienced at least 1 episode of elevated IOP in the adjunct group, but development of glaucoma (confirmed by a glaucoma subspecialist) was similar between the 2 groups.

Study Limitations

Our study has limitations that must be acknowledged. It was not possible to mask the investigators, because the IMP was sometimes visible on posterior chamber assessment. However, efforts were made to minimize investigator bias by masking the operating surgeon until the end of the operative procedure and by adhering to explicit management protocols (e.g., elevated IOP). Furthermore, some outcome assessments were objective through automation (SD OCT foveal thickness and volume), and the binary nature of the primary outcome is less susceptible to bias. Also, given the heterogeneous nature of the cohort, we accept the limitations of detecting small differences between the 2 groups. Nevertheless, the study was designed to be pragmatic and as inclusive as possible to reflect clinical practice.

This is the first published randomized controlled clinical trial to use a slow-release dexamethasone implant in eyes with established PVR. We found no difference in anatomic retinal reattachment and PVR recurrence rates at 6 months; however, we did observe an apparent treatment effect of reduced postoperative cystoid macular edema. Further clinical trials are indicated to identify pharmacologic agents aimed at improving anatomic and visual outcomes in eyes with PVR, but this study suggests that there is a greater reduction in CMO observed at 6 months in vitrectomized eyes treated with slow-release dexamethasone.

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Overall responsibility: Banerjee, Quartilho, Bunce, Xing, Zvobgo, Harris, Charteris

Abbreviations and Acronyms:
AE = adverse event; **CI** = confidence interval; **CMO** = cystoid macular edema; **DMC** = Data Monitoring Committee; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IMP** = investigational medicinal product; **IOP** = intraocular pressure; **IQR** = interquartile range; **logMAR** = logarithm of the minimum angle of resolution; **OR** = odds ratio; **PVR** = proliferative vitreoretinopathy; **SD** = standard deviation; **SD OCT** = spectral domain optical coherence tomography; **VA** = visual acuity.

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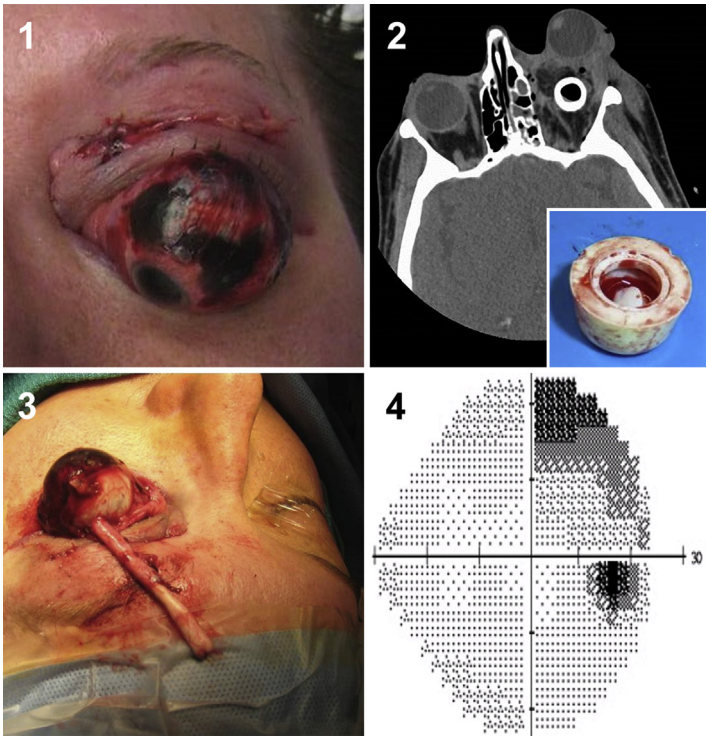
Pictures & Perspectives



Traumatic Enucleation with Chiasmal Damage

A 45-year-old woman presented with traumatic enucleation of the left eye (Figs 1, 2) following a syncopal episode that led to a fall onto a mounted door stop. Surgical repair consisted of an orbitotomy with removal of the retained rubber door stop (Fig 2, *insert*), removal of the eyeball and a long segment of avulsed optic nerve (Fig 3), and repair of an upper eyelid laceration. A follow-up visual field of the right eye revealed a temporal visual defect consistent with chiasmal damage (Fig 4).

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