Slow-release dexamethasone in proliferative vitreoretinopathy; a prospective randomised controlled clinical trial

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Abstract

Purpose: To test the hypothesis that adjunctive slow release dexamethasone implant (Ozurdex ®) can improve the outcomes of vitreoretinal surgery for established PVR

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

Subjects: One hundred and forty patients requiring vitrectomy surgery with silicone oil for retinal detachment with established PVR (Grade C) were randomized to either standard (control) or study treatment (adjunct) in a 1:1 allocation ratio.

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

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 i) final visual acuity (median and ETDRS of 55 letters or better), ii) cystoid macular edema (CMO), foveal thickness and macular volume iii) development of overt PVR recurrence, iv) complete and posterior retinal reattachment, vi) tractional retinal detachment, vii) hypotony/raised IOP, viii) macula pucker/epiretinal membrane, ix) cataract, x) 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 anatomical success between the two groups (49.3% vs 46.3%, adjunct vs control, (Odds Ratio 0.89, 95% Confidence interval 0.46 – 1.74, p= 0.733). Mean visual acuity at 6 months was 38.3 ETDRS letters and 40.2 letters in the adjunct and control group respectively. Secondary anatomical outcomes

(complete/posterior reattachment rates and PVR recurrence) were comparable between the two groups. At 6 months, fewer adjunct patients had CMO (42.7%) or a foveal thickness of >300µm (47.6%) compared to controls (67.2% and 67.7%, respectively p= 0.004,p= 0.023).

Conclusion: A slow-release dexamethasone implant does not improve the primary anatomical success rate in eyes undergoing vitrectomy surgery with silicone oil for PVR. Further clinical trials are indicated to improve anatomical and visual outcomes in these eyes, but this study suggests that there is a greater reduction in CMO observed at six months in vitrectomised eyes treated with slow-release dexamethasone.

Introduction

Proliferative vitreoretinopathy (PVR) is the most common cause of late anatomic failure following vitrectomy for rhegmatogenous retinal detachment. Its reported incidence ranges from 5-11% of all rhegmatogenous retinal detachments[1]. PVR can be considered a maladapted wound healing retinal response in which cellular proliferation, migration and deposition results 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, and/or tractional retinal detachment, with the reopening of pre-existing breaks or the formation of new ones.

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

Experimentally, corticosteroids can potentially influence both the inflammatory and proliferative components of the PVR process via a variety of modes of administration [13, 14 15] without evidence of demonstrable retinal toxicity [16].

Clinically, intravitreal crystalline cortisone was first reported in 2000 by Jonas *et al* to be well tolerated in PVR cases undergoing vitrectomy. [17] 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 0.7mg slow-release preparation of dexamethasone given at the time of vitrectomy surgery and repeated at the time of oil removal, could improve anatomical and visual outcomes in eyes with PVR.

Patients and Methods

This phase IIIb, single-centre, participant-masked, prospective randomised controlled clinical trial was performed at Moorfields Eye Hospital NHS Foundation Trust between February 2012 and February 2015 [22]. Prior to participant recruitment, Moorfields Research Management Committee approval was obtained, a favourable opinion from the National Research and Ethics Service Committee London - Central was received (11/LO/1685) and the study was granted a clinical trials authorisation by the MHRA. 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 (TSC) provided study oversight throughout the duration of the trial.

Participants

The study population consisted of male and female patients aged 18 years and over. 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: a) open globe injury b) 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 raised IOP) c) uncontrolled uveitis, d) previous steroid induced glaucoma, e) proliferative diabetic retinopathy or vasculopathy, f) pregnant or breastfeeding females, g) previous known adverse reaction to the Ozurdex®, h) suspected ocular/periocular infection (e.g Herpes Simples Virus, Varicella Zoster Virus, mycobacterial, fungal disease, i) aphakia or patients in whom a lensectomy is planned at time of surgery, j) pre-existing anterior chamber intraocular lens.

There were no restrictions on the number of previous vitreoretinal procedures.

Randomisation

A randomization schedule of 140 treatment allocations against 140 study IDs was produced by a statistician using random permuted blocks of varying sizes. The randomisation schedule was provided to the clinical trials pharmacy at the study site, who prepared treatment packs according to the randomisation schedule. Upon 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. 70 patients were randomised to receive standard surgical care (Control

Group) and 70 patients were randomised to receive standard surgical care in addition to the supplementary adjunctive dexamethasone implant (Adjunct Group).

Intervention

Both groups received the standard vitreoretinal operative procedure which their ocular condition required. Consultants or senior fellows (2nd year fellowship) performed the operative procedures.

ADJUNCT GROUP

Upon 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 0.7mg slow release dexamethasone implant through the final open sclerotomy port prior to suturing.

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

CONTROL GROUP

Following 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 upon exit. Additionally, 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, as the primary 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 NIHR Clinical Research Facility at Moorfields Eye Hospital (PB, DC or MZ); day 1, day 10, 4-6 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 (ETDRS chart) applanation tonometry and anterior segment assessment were recorded. Spectral domain optical coherence tomography (SD-OCT) (Heidelberg) 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.

Two additional study visits at Days 60 post 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 (AE)

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

Secondary outcomes

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

i) visual acuity (a comparison of the mean/median visual acuity and the proportion of patients in each group achieving a VA of 55 ETDRS letters or better)

ii) macula edema and thickness (OCT analysis) i.e the proportion of patients in each group with a central A1 macula subfield measure of >300um

iii) the proportion of patients in each group who develop overt PVR recurrence

iv) the proportion of patients in each group achieving complete retinal reattachment

v) the proportion of patients in each group achieving stable posterior (post equatorial) retinal reattachment

vi) the proportion of patients in each group with a tractional retinal detachment

vii) the proportion of patients in each group who suffer hypotony (defined as IOP <6mmHg and/or raised IOP (defined as >25mmHg) at any timepoint during the study period

viii) the proportion of patients in each group who develop the presence of macula pucker/epiretinal membrane and/or require macula ERM surgery at any time point during the study

ix) the proportion of patients in each group who require cataract surgery at any time point during the study

x) Quality of Life assessment – a comparison in the median/mean scores of both SF36 and VFQ between both groups

Sample size

Based on the results of the primary outcome measure from a trial of the same patient group carried out in the study centre [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 regime (reducing failure from 49% to 24%). This reduction in failure rate was deemed clinically meaningful. 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 categorical variables.

Analysis was conducted following the intention to treat (ITT) principle. An available case analysis was conducted together with best/worst case scenario imputation analysis and results 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 presented were 95% and two-sided.

The primary outcome was reported by treatment group with 95% confidence intervals (CI) 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 were also computed by PVR severity (severe i.e. CA or CP > 4 versus less severe i.e. CA and CP ≤ 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 difference between treatment arms in change from baseline in continuous variables (e.g. visual acuity, quality of life).

Sensitivity analysis was conducted using analysis of covariance to explore difference between treatment arms in change from baseline in visual acuity 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 (PJB) masked to treatment allocation and outcome.

The proportion of patients who experience an AE or SAE was reported by event type and treatment group.

A post-hoc exploratory analysis was conducted on patients with available quantitative SD-OCT readings at 6 months, using chi-squared tests to compare the proportion of patients with 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. One hundred and ninety two patients were assessed for eligibility of which 29 were ineligible and excluded. Of the remaining 163 eligible patients, 20 patients declined to participate in the study. Three further patients enrolled in the study but were not randomized as silicone oil was not used. The remaining one hundred and forty 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 non-ocular characteristics are summarized in table 1 showing comparable gender, mean age, and ethnicity, with a Caucasian 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 having suffered 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 co-morbidity compared to the control group (n=10). These included a history of amblyopia, age-related macular degenerative disease and closed globe ocular trauma.

The median presenting visual acuity was zero ETDRS letters (i.e ≤ Counting Fingers) in both groups, and mean intra-ocular pressure readings were 11.9mmHg and 13.3mmHg in the adjunct and control group, respectively. Baseline markers of inflammation and blood ocular barrier breakdown

(anterior chamber cells, vitreous haemorrhage and RPE cells) were comparable between the two groups.

Thirty seven (52.9%) of the adjunct group patients were pseudophakic compared to thirty four (48.6%) control patients. Of the remainder, the majority showed signs of lens opacity with approximately ten percent 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 duration of retinal detachment was 25 and 21 days in the adjunct and control group, respectively. The median extent of retinal detachment was comparable, with eight clock hours of RD recorded in the adjunct group and nine in the control arm. The median grades of anterior and posterior PVR (as assessed intraoperatively) were comparable between the two groups.

Operative Techniques

Table 4 outlines the operative techniques employed during the primary study vitrectomy. 38 (54.3%) adjunct patients and 39 (55.7%) control patients underwent a retinectomy at the time of their primary study vitrectomy.

Primary Outcome Measure

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

There was no observed difference in primary outcome between the two groups (Table 5): 49% of patients (n= 34 of 69) in the adjunct group achieved a stable retinal reattachment with silicone oil removal without additional vitreoretinal surgical intervention at 6 months, compared to 46% (n=32 of 69) in the control group. (Odds Ratio (OR) 0.89, 95% Confidence interval 0.46 – 1.74, p= 0.733 Chi Squared). Best case and worst case imputation analysis did not affect the primary outcome findings. Sub-group analysis stratifying by severity of PVR (Grade CP or CA > 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 post study vitrectomy. Six month outcome measures are included in this report (tables 6 to 8) and are reported on 138 of 140 patients unless otherwise stated in the table. Twelve month secondary outcome measures will be described in subsequent reports.

Visual Acuity (Table 6)

At six months following study vitrectomy, mean visual acuity was comparable between the two treatments: 38.3 ETDRS letters (standard deviation 23.7) in the adjunct group compared to 40.2 letters (standard deviation 21.1) in the control group. A sensitivity analysis excluding eyes with pre-existing ocular co-morbidity limiting visual outcome was performed and did not affect the findings. The proportion of eyes achieving a visual acuity ≥ 55 ETDRS letters was also comparable, with 21 of 69 eyes (30%) in the adjunct group achieving this vision or better, compared to 17 of 69 eyes (24%) in the control group.

Secondary Anatomical Outcomes (Table 7)

At 6 months, the proportion of patients achieving complete retinal reattachment or a stable posterior retinal reattachment was comparable between the two treatment groups. Similarly, the proportion of patients with a tractional retinal detachment at 6 months was also comparable. The rate of overt PVR recurrence (defined as the presence of postoperative PVR at any timepoint up to 6 months post 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 one operation to achieve success in the control group compared to 3 patients (4.4%) in the adjunct group.

Macular Findings (Table 8)

At six months, for patients with available quantitative SD-OCT readings, median foveal thickness and macular volume were lower in the adjunct group (297µm and 8.85mm^3) compared to the control group (365µm and 9.23 mm^3). Similarly, the proportion of eyes with a foveal thickness >300µm in the A1 macular subfield was lower in the adjunct group (n=30, 47.6 %) compared to the control group (n=42, 67.7%) (OR = 2.3, 95% CI 1.12 – 4.78, p= 0.023), Chi Squared). Furthermore the proportion of eyes with macular oedema in the adjunct group was 42.7% (n=29) compared to 67.2% (n=45), (OR = 2.8, 95% CI 1.37 – 5.54, p= 0.004, Chi Squared).

40 patients (57.1%) in the adjunct group and 41 patients (58.6%) in the control group developed macular ERM at any timepoint up to 6 months, with comparable rates of macular pucker surgery between the two groups.

Cataract and IOP Outcomes

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

Rates of hypotony were also similar between the two groups, with 20% of patients (n=14) in the adjunct group suffering at least one episode of hypotony and 24.3% (n=17) in the control group. The median and interquartile range 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 one episode of elevated IOP compared to the control group (n=22, 31.4%).

Quality of Life Parameters

Mean SF6 and VFQ-25 scores and mean change from baseline showed no evidence of a difference between the two treatment groups (supplementary Table 3).

Adverse Events (AE) and Serious Adverse Events (SAE)

There were no serious adverse reactions observed in either group. AEs are displayed in supplementary table 1 (online supplementary file) and totalled 595 episodes, with 285 events in

the adjunct group compared to 310 in the control group. 66 of 70 (94.3%) adjunct patients suffered at least one AE compared to 63 of 70 (90.0%) of control patients.

The most common AE was elevated IOP. In the adjunct group there were 85 episodes (39.2%) of raised IOP compared to 75 (31.4%) in the control group. There were 17 serious adverse events during the study (16 non-ocular and one ocular), which were comparably distributed between the two groups (supplementary table 2). The ocular SAE 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 to the adjunct group (n=10).

Discussion

Dexamethasone has a potency which is five 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 6mm implant containing 700µg of dexamethasone in a biodegradable polymer (Novadur™, Allergan, Irvine, CA, USA). It exhibits a dual-phase response of initially high concentrations of dexamethasone in the first two months, followed by a period of lower concentrations sustained for up to 6 months post-injection[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 non-infectious posterior uveitis [32]. Its market authorisation was subsequently expanded in 2014 to include patients with diabetic macular edema [33].

This is the first randomised controlled clinical trial (RCT) investigating the use of a slow-release preparation of corticosteroid in proliferative vitreoretinopathy. Recruitment was completed within the projected timescale and study retention rate was favourable at 98.6%. To date there have been eight RCTs [4, 6-8, 10, 34-36] investigating a variety of pharmacological 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 RCTs adopting a comparable primary outcome measure [7, 36]. In a study comparing the effect of 4mg 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.

If we consider secondary outcomes indicative of the effect of the IMP on the PVR process, we found only limited evidence of differences between the two 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 also similar between the two 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 two or more operations to achieve attachment compared to the control group (n=11). However, as this was not investigated

as a secondary outcome and numbers are small, we did not test for statistical significance, and caution must therefore 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 oedema at 6 months in the adjunct group (42.7%, n=29) compared to 67.2% (n=45) in the control group. Similarly the proportion of eyes with a central foveal thickness of > 300µm in the A1 subfield was statistically significantly lower in the adjunct group (47.6%) in comparison to 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 ERM may also affect foveal thickness. Our findings are consistent with previous reports that a slow-release dexamethasone implant may be an effective treatment for CMO in vitrectomised eyes. Boyer *et al* [37] reported a statistically significant reduction in diabetic macular oedema with corresponding visual improvement up to six months post implant injection in fifty-five vitrectomised eyes. Furthermore, other authors have reported that the same slow-release preparation has successfully treated refractory macular oedema secondary to uveitis, venous occlusions, and following vitrectomy for retained lens fragments [38-40].

Despite observing a difference in rates of postoperative CMO, we did not observe any difference in visual acuity (VA) at six months. The mean VA in the adjunct group was 38.3 ETDRS letters (standard deviation 23.7) compared to 40.2 letters (standard deviation 21.1) in the control group. This equates to LogMAR VAs of 0.96 and 0.90, and approximates to a Snellen VA of 20/160. Similarly, the proportion of eyes achieving a visual acuity ≥ 55 ETDRS letters (> 20/80) was also comparable (30.4% vs 24.6%, adjunct vs control). Mean final postoperative visual acuity 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 favourably to previous reports, however, a study investigating poor visual outcomes (< 20/40) after successful RD repair for PVR in thirty five 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 remodelling [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 following RD surgery in eyes with PVR. SD-OCT imaging of eyes following fovea-involving RDs (without PVR) have correlated outer retinal abnormalities with poorer visual outcomes [43-46], and thus may serve as a target for investigation in future studies.

Overall, we observed a higher number of adverse events 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 one episode of elevated IOP in the adjunct group but development of glaucoma (confirmed by a glaucoma subspecialist) was similar between the two groups. Our study has limitations which must be acknowledged. It was not possible to mask the investigators, as the IMP was sometimes visible on posterior chamber assessment. However, efforts were made to minimise 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. Additionally, given the heterogenous nature of the cohort, we

accept the limitations of detecting small differences between the two groups. Nevertheless, the study was designed to be pragmatic and as inclusive as possible, so as to reflect clinical practice.

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

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Table 1. Non-Ocular Baseline Characteristics

	Adjunct Group (N=70)	**Control Group (N=70)**
Number 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 for:		
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)*

VFQ 25 = visual functioning 25point questionnaire, SF 36 = social functioning 36 point questionnaire, IQR interquartile range

Table 2a. Baseline Ocular Characteristics (Non-Retinal)

	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, 0)	0 (-2.63, 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)
Co-existing 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

SE = spherical equivalent, V/Gas = vitrectomy/gas, V/oil = vitrectomy/oil, V/B = vitrectomy/buckle, C/B = cryotherapy/buckle, OHT = Ocular hypertension, mac off episodes = know episodes of fovea-involving retinal detachments

Table 2b. Baseline Ocular Characteristics (Non-Retinal)

	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 Haemorrhage, n (%)		
Absent	66 (94.3)	67 (95.7)
Present	4 (5.7)	3 (4.3)

BCVA = Best Corrected Visual Acuity, IOP= Intraocular Pressure, AC = anterior chamber, PCIOL = posterior chamber intraocular lens, ACIOL = anterior chamber intraocular lens.* AC inflammation cell count according to SUN classification

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)

RD = Retinal Detachment, PVR = Proliferative vitreoretinopathy, CP = posterior Grade C, CA = anterior Grade C
*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)

PVD = Posterior Vitreous Detachment, PFCL = Perfluorocarbon

Table 5. Primary Outcome Result (Available ITT analysis)

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

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 months**	38.3 (23.7)	40.2 (21.1)	-
- **Change from baseline at 6 months***	24.5 (28.6)	23.1 (26)	1.1 (-6.3, 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 months**	41.60 (23.1)	41 (20.9)	-
- **Change from baseline at 6 months***	26.4 (29.3)	23.2 (26.4)	-1.2 (-8.8, 6.4)

* Adjusted for respective baseline, BCVA = Best Corrected Visual Acuity

Table 7. Secondary Outcome Measures; Anatomical 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)
Number 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)

* Between the primary study vitrectomy and 6 months, ** without silicone oil in situ

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 to 5.54, p = 0.004)
**** FT > 300 µm, n (%)**	30 (47.6)	42 (67.7)	2.3 (1.12 to 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)	-

* % expressed as proportion of available cases (68 eyes in adjunct group 67 eyes control group), ** % expressed as proportion of available cases (63 eyes adjunct group, 62 eyes control) † % expressed as proportion of n=70

Supplementary Table 1. Adverse Events (AEs)

	Adjunct Group (N=70)	Control Group (N=70)
Total number of AEs, n	285	310
Number of expected AEs: n (%*)		
Cataract	0 (0)	1 (0.42)
Raised IOP	85(39.2)	75 (31.4)
Hypotony	27 (12.4)	31 (13)
Sterile Hypopyon	0 (0)	1 (0.4)
Retinal Detachment	45 (20.7)	51 (21.3)
Uveitis	10 (4.6)	24 (10)
Further Surgery	41 (18.9)	51 (21.3)
Glaucoma	3 (1.4)	2 (0.8)
Headache	5 (2.3)	1 (0.4)
Migraine	1 (0.5)	2 (0.8)
Vitreous Opacities	0 (0)	0 (0)
Tractional Maculopathy	0 (0)	0 (0)
Number of unexpected AEs: n (%)		
Systemic Illness	15 (22)	18 (25.4)
Ocular Vascular Occlusion	3 (4.4)	3 (4)
Raised Blood Pressure	6 (8.8)	6 (8.5)
Iris Bombe	6 (8.8)	6 (8.5)
Fellow Eye RD Surgery*, n (%) ***Number of patients, n (%)***	2 (2.9) *1 (1.5)*	1 (1.4) *1 (1.6)*
Other (Ocular), n (%)	10 (14.7)	17 (23.9)
Other (Non-Ocular), n (%)	26 (38.2)	20 (28.2)

(Percentages calculated in relation to total number of Expected and unexpected AEs in each group)

Supplementary Table 2 Serious Adverse Events (SAEs)

	Adjunct Group (N=70)	Control Group (N=70)
Total number of patients with at least one SAE, n	7	6
Total number SAEs	10	7
Number of unexpected SAEs: n (%)		
Systemic Illness, n (%)	9 (90)	4 (57)
Other (Ocular), n (%)	1(10)	0 (0)
Other (Non-Ocular), n (%)	0 (0)	3 (42.9)

(Percentage calculated in relation to total number of SAE in each group)

Supplementary Table 3. Quality of Life Outcome Measures at 6 months

	Adjunct Group (N=69)	Control Group (N=69)	Effect Estimate (95% CI, p value)
Score for:			
VFQ 25, mean (SD)			
- **At 6 months**	66.4 (17.7)	66 (18)	
- **Change from baseline at 6 months***	3.6 (15.6)	1.9 (11.8)	-1.3 (-5.7, 3.1)
Missing (change), n (%)	*1 (1.4)*	*3 (4.3)*	
SF 36, mean (SD)			
- **At 6 months**	64.8 (22.2)	71.3 (19.5)	
- **Change from baseline at 6 months***	2.8 (21.7)	3.5 (18.3)	3.1 (-3.1, 9.3)
Missing (change), n (%)	*1 (1.4)*	*3 (4.3)*	

Figure 1. Ozurdex in PVR Consort Diagram