Clinical science

Randomised controlled trial of adjunctive triamcinolone acetonide in eyes undergoing vitreoretinal surgery following open globe trauma: The ASCOT study

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ABSTRACT

Background/aims To investigate the clinical effectiveness of adjunctive triamcinolone acetonide (TA) given at the time of vitreoretinal surgery following open globe trauma (OGT).

Methods A phase 3, multicentre, double-masked randomised controlled trial of patients undergoing vitrectomy following OGT comparing adjunctive TA (intravitreal and subtenons) against standard care (2014–2020). The primary outcome was the proportion of patients with at least 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letter improvement in corrected visual acuity (VA) at 6 months. Secondary outcomes included: change in ETDRS, retinal detachment (RD) secondary to PVR, retinal reattachment, macular reattachment, tractional RD, number of operations, hypotony, elevated intraocular pressure and quality of life.

Results 280 patients were randomised over 75 months, of which 259 completed the study. 46.9% (n=61/130) of patients in the treatment group had a 10-letter improvement in VA compared with 43.4% (n=56/129) of the control group (difference 3.5% (95% CI −8.6% to 15.6%), OR=1.03 (95% CI 0.61 to 1.75), p=0.908)). Secondary outcome measures also failed to show any treatment benefit. For two of the secondary outcome measures, stable complete retinal and macular reattachment, outcomes were worse in the treatment group compared with controls, respectively, 51.6% (n=65/126) vs 64.2% (n=79/123), OR=0.59 (95% CI 0.36 to 0.99), and 54.0% (n=68/126) vs 66.7% (n=82/123), OR=0.59 (95% CI 0.35 to 0.98), for TA vs control.

Conclusion The use of combined intraocular and sub-Tenons capsule TA is not recommended as an adjunct to vitrectomy surgery following OGT.

Trial registration number NCT02873026.

WHAT IS ALREADY KNOWN ON THE TOPIC

⇒ Proliferative vitreoretinopathy (PVR) is the most common cause of recurrent retinal detachment in eyes following open globe trauma.

WHAT THIS STUDY ADDS

⇒ Adjuvant triamcinolone did not improve visual outcomes at the time of vitrectomy following open globe trauma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study adds to the evidence surrounding the treatment of PVR but was limited perhaps by its broad inclusion criteria. Future PVR trial designs will need to have a clear focus on disease categorisation and the timing of intervention.

INTRODUCTION

Ocular trauma is a leading cause of visual loss worldwide and is the most common cause of unilateral visual loss, with significant socioeconomic implications.[1] In eyes that suffer open globe trauma (OGT), retinal detachment is a frequent complication and often requires multiple surgical procedures.[2 3] Proliferative vitreoretinopathy (PVR) is the most common cause of recurrent retinal detachment in these eyes and is associated with a worse visual outcome.[4]

Corticosteroid treatment has the potential to reduce the inflammatory and proliferative components of PVR; laboratory studies have suggested that corticosteroids can downregulate the pathobiological processes of PVR development.[5–7] A previous pilot randomised controlled study suggested that the adjuvant use of corticosteroid at the time of vitrectomy in eyes that had suffered OGT was associated with an improvement in visual outcomes.[8] A randomised controlled trial (RCT) on slow-release dexamethasone in vitreoretinal surgery also suggested a positive effect from steroid adjuncts in PVR cases,[9] although other studies using oral steroids have not shown an effect.[10]

The aim of this study was to test the hypothesis that adjunctive triamcinolone acetonide (TA), given at the time of surgery, can improve the outcome of vitreoretinal surgery following open globe

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trauma. The study analysed its effect on VA and the incidence of re-detachment.

METHODS

A phase 3 multicentre double-masked RCT was carried out between November 2014 and September 2020. The trial was registered on the Clinicaltrials.gov database on 19 August 2016. The study complied at all times with the tenets of the Declaration of Helsinki. Patients provided written informed consent before enrolment. An independent Data Monitoring Committee and Trial Steering Committee provided oversight throughout the trial. The full study protocol is detailed elsewhere.[11] During the trial, the protocol was amended to change the primary outcome from a dual outcome to a single outcome (proportion of patients with a greater than 10 letter Early Treatment Diabetic Retinopathy Study (ETDRS) letter score improvement). The co-primary outcome, ETDRS letter score at 6 months, was converted to a principle secondary outcome. This was because it was felt that ETDRS letter score would have an unusual distribution, therefore requiring a complex statistical model which may be more difficult to communicate and that a binary outcome was more clinically meaningful to clinicians and patients.

Participants

Eligible patients were those over 18 years old who had suffered full-thickness OGT and were undergoing vitrectomy, able to give written consent, willing to accept randomisation and able to attend 6-month follow-up. Exclusion criteria were (1) age under 18 years old; (2) pre-existing uncontrolled uveitis; (3) previous diagnosis of steroid-induced glaucoma; (4) pregnant or breast-feeding women; (5) allergy or previous reaction to TA; (6) inability to attend follow-up; (7) inability to give written consent; (8) current or planned systemic corticosteroid use of a dose above physiological levels (>10 mg prednisolone). The indication for vitrectomy following OGT was at the discretion of the operating surgeon.

Recruitment

The multicentre study was planned across 20 UK sites. Recruitment was monitored and seven more recruiting sites were added during the trial.

Intervention

Both groups received standard surgical treatment and routine preoperative and postoperative treatment and care. Standard care involved vitrectomy, treatment of retinal detachment if present and the surgeon's choice of intraocular tamponade agent. The Adjunct Group received additional postoperative steroid combination (triamcinolone acetonide, Kenalog, E.R. Squibb & Sons, New York, USA) consisting of 4 mg/0.1 mL into the vitreous cavity and 40 mg/1 mL subtenons. The control group received standard care only.

Randomisation, masking and assessments

Eligible participants were randomised (1:1) using a telephone service to the Emergency Scientific Medical Services global service hosted at the King's College Clinical Trials Unit. The randomisation assignments were created using permuted blocks of varying sizes with stratification by trial centre. Randomisation and treatment allocation were performed intraoperatively once the operating surgeon had confirmed that the retina was attached. Operating surgeons were masked until the end of surgery; participants and study investigators were masked to treatment allocation throughout. The trial statistician remained subgroup masked throughout the trial and analysis.

Baseline assessments were performed within 14 days prior to the study vitrectomy. Participants' study visits were at 3 and 6 months postoperatively. Adverse events were reported to the sponsor as per the study protocol. Elevated intraocular pressure was defined as >25 mm Hg.

Outcomes

The primary outcome was the proportion of patients with an improvement from baseline to 6 months of at least 10 on the corrected VA (ETDRS letter score at a starting distance of 4 m) in the study eye. The secondary outcomes were (1) change in corrected VA score (ETDRS letter score) at 6 months after initial study surgery; (2) retinal detachment with PVR at any timepoint within 6 months; (3) stable complete retinal reattachment (without internal tamponade present) at 6 months; (4) stable macular retinal reattachment (without internal tamponade present) at 6 months; (5) tractional retinal detachment at any timepoint within 6 months; (6) the number of operations to achieve stable retinal reattachment (either complete or macula) at 6 months; (7) hypotony (<6 mm Hg) at any timepoint within 6 months; (8) raised intraocular pressure (>25 mm Hg) at any timepoint within 6 months; (9) macular pucker by 3 and 6 months and/or require macular pucker surgery at any timepoint within 6 months; (10) quality of life measured using the VFQ25, CSRI and the EQ-5D-5L questionnaire.

Sample size

The target sample size was 300 (150 per arm) over a 3-and-a-half-year recruitment period. This was based on an assumed proportion of individuals with clinically meaningful

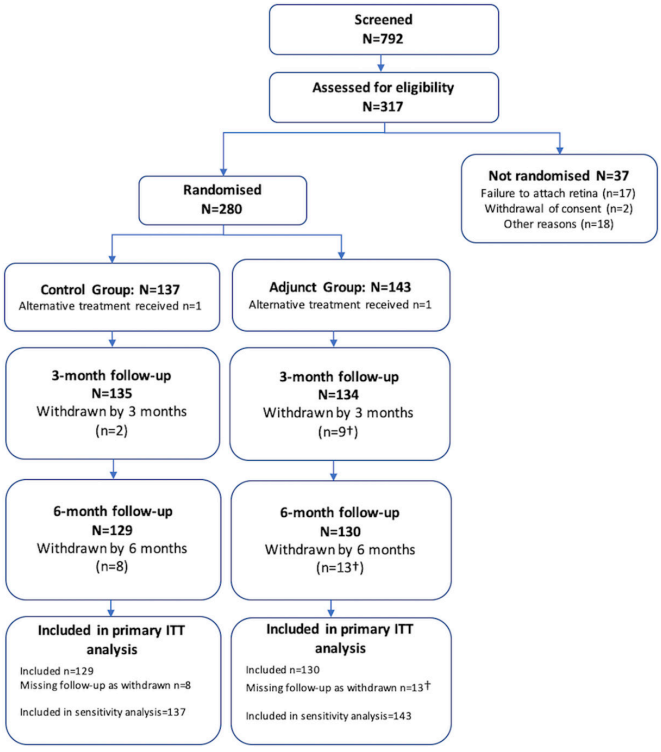

Figure 1 CONSORT diagram. CONSORT diagram shown for the Ascot study. †Four participants who were randomised in error as ineligible and immediately withdrawn on date of randomisation. Numbers withdrawn are cumulative. ITT, intention on treat.

Table 1 Baseline demographics

Characteristic	Control n=137	Missing	Adjunct n=143	Missing	Total n=280	Missing
Gender						
Male	123 (90%)	0	123 (86%)	0	246 (88%)	0
Ethnicity						
White	113 (82%)	0	120 (84%)	0	233 (83%)	0
Black	11 (8%)		9 (6%)		20 (7%)	
Asian	7 (5%)		11 (8%)		18 (6%)	
Other	3 (2%)		3 (2%)		6 (2%)	
Mixed	3 (2%)		0		3 (1%)	
Current smoker	55 (41%)	4	51 (36%)	3	106 (39%)	7
Eye injured						
Right	67 (49%)	0	70 (49%)	0	137 (49%)	0
Left	66 (48%)		72 (50%)		138 (49%)	
Both	4 (3%)		1 (1%)		5 (2%)	
Glaucoma	2 (1%)	1	2 (1%)	0	4 (1%)	1
Previous eye surgery	67 (49%)	0	82 (57%)	0	149 (53%)	0
Macular disease	0	1	1 (1%)	0	1 (<1%)	1
Mechanism of injury						
Workplace incident	40 (29%)	0	48 (34%)	0	88 (32%)	0
Road traffic accident	5 (4%)		6 (4%)		11 (4%)	
Interpersonal violence	33 (24%)		33 (23%)		66 (24%)	
Sports injury	5 (4%)		5 (3%)		10 (4%)	
Other Injury	16 (12%)		21 (15%)		37 (13%)	
Other domestic	11 (8%)		10 (7%)		21 (8%)	
Domestic gardening	5 (4%)		3 (2%)		8 (3%)	
Domestic DIY	10 (7%)		3 (2%)		13 (5%)	
Iatrogenic	0		3 (2%)		3 (1%)	
Fall	12 (9%)		11 (8%)		23 (8%)	
Previous primary repair	95 (69%)	0	110 (77%)	1	205 (73%)	1
Time since primary repair (days)						
Median (IQR)	28 (12–151)		26 (11–108)		27 (12–119)	
Classification of Injury						
Rupture	53 (39%)	0	60 (42%)	0	113 (40%)	0
Penetrating	51 (37%)		52 (36%)		103 (37%)	
Perforating	4 (3%)		7 (5%)		11 (4%)	
IOFB	29 (21%)		24 (17%)		53 (19%)	
Extent of injury						
Zone 1 (cornea)	51 (38%)	2	44 (31%)	1	95 (34%)	3
Zone 2 (limbus to muscle insertion)	56 (41%)		54 (38%)		110 (40%)	
Zone 3 (posterior to muscle insertion)	28 (21%)		44 (31%)		72 (26%)	
RAPD						
Present	17 (13%)	2	26 (18%)	0	43 (15%)	2
Not documented	69 (51%)		71 (50%)		140 (50%)	
Visual axis corneal scar	32 (23%)	0	40 (28%)	0	72 (26%)	0
Uveitis	26 (19%)	0	26 (18%)	0	52 (19%)	0
Hyphaemia						
Absent	96 (70%)	0	90 (63%)	0	186 (66%)	0
<50%	24 (18%)		26 (18%)		50 (18%)	
>50%	17 (12%)		27 (19%)		44 (16%)	
Iris						
Normal	52 (39%)	2	59 (42%)	2	111 (40%)	4
Incomplete	63 (47%)		72 (51%)		135 (49%)	
Incarcerated	20 (15%)		10 (7%)		30 (11%)	
Lens						
Clear	37 (27%)	1	33 (24%)	2	70 (25%)	3
Cataract	46 (34%)		50 (36%)		96 (35%)	
ACIOL	0		2 (1%)		2 (1%)	

Continued

Table 1 Continued

Characteristic	Control n=137	Missing	Adjunct n=143	Missing	Total n=280	Missing
PCIOL	12 (9%)		8 (6%)		20 (7%)	
Aphakic	41 (30%)		48 (34%)		89 (32%)	
Vitreous haemorrhage	85 (63%)	2	97 (69%)	2	182 (66%)	4
Endophthalmitis	2 (1%)	1	3 (2%)	0	5 (2%)	1
Retinal detachment						
TRD	17 (12%)	0	21 (15%)	0	38 (14%)	0
RRD	49 (36%)		56 (39%)		105 (38%)	
Absent	71 (52%)		66 (46%)		137 (49%)	
Fovea involved? (TRD and RRD only)						
Yes	41 (62%)	0	44 (57%)	0	85 (59%)	0
Splitting	0		1 (1%)		1 (1%)	
No	25 (38%)		32 (42%)		57 (40%)	
IOFB						
None	101 (74%)	0	118 (83%)	0	219 (78%)	0
Intravitreal	13 (9%)		18 (13%)		31 (11%)	
Intraretinal	19 (14%)		7 (5%)		26 (9%)	
Intrascleral	4 (3%)		0		4 (1%)	
Presence of retinal incarceration	25 (18%)	0	38 (27%)	0	63 (23%)	0
Presence of PVR C	29 (21%)	0	38 (27%)	1	67 (24%)	1
Age (years)						
Mean (SD)	42.7 (15.3)	0	46.8 (17.3)	0	44.8 (16.5)	0
ETDRS VA in study eye (total score)						
Mean, SD	16.6 (30.5)	0	10.4 (23.6)	0	13.4 (27.3)	0
Median, IQR	0.0 (0.0–11.0)		0.0 (0.0–0.0)		0.0 (0.0–1.0)	
Zero/very low	98 (72%)		111 (78%)		209 (75%)	
>0	39 (28%)		32 (22%)		71 (25%)	
Where zero/very low, vision:						
Counting finger	10 (10%)		9 (8%)		19 (9%)	
Hand movement	60 (61%)		54 (49%)		114 (55%)	
Perception light	26 (27%)		45 (41%)		71 (34%)	
No perception light	2 (2%)		3 (3%)		5 (2%)	
Where ETDRS VA>0						
Mean, SD	58.3 (28.9)		46.6 (28.4)		53.0 (29.1)	
Median, IQR	64.0 (45.0–83.0)		48.0 (21.0–66.0)		58.0 (24.0–80.0)	
IOP in study eye						
Mean (SD)	12.4 (7.4)	14	11.7 (6.4)	12	12.0 (6.9)	26
Low	92 (75%)		103 (79%)		195 (77%)	
Normal	21 (17%)		18 (14%)		39 (15%)	
High	10 (8%)		10 (8%)		20 (8%)	

ACIOL, anterior chamber intraocular lens; ETDRS, Early Treatment Diabetic Retinopathy Study; IOFB, intraocular foreign body; IOP, intraocular pressure; PCIOL, posterior chamber intraocular lens; PVR, proliferative vitreoretinopathy; RAPD, relative afferent pupillary defect; RRD, rhegmatogenous retinal detachment; TRD, tractional retinal detachment; VA, visual acuity.

improvement in VA (>10 letters) of 55% in the standard care arm and a 19% increase in the adjunct group to 75%, with approximately 7% loss to follow-up, at least 90% power and two-sided 5% type 1 error. Following slower than anticipated recruitment, the recruitment period was extended to 75 months. Over the full recruitment period, 280 eligible patients were recruited and are included within this analysis. Based on the original sample size parameters outlined above, it was established that the trial would still be adequately powered: a sample size of 280, assuming loss to follow-up of 7%, that is, 260 completers at 6 months provided 89.7% power to detect a 19% increase (55%–74%) in meaningful improvement in VA (>10 letters).

Statistical analysis

Analysis was conducted subgroup masked (ie, group A vs B) following the ASCOT statistical analysis plan.[12] The main analysis was based on the intention-to-treat principle and included all eligible participants with follow-up in their randomised group to estimate the effect of the treatment policy (see online supplemental file). The primary analysis model consisted of a mixed logistic model with change in VA (<10, ≥10 change in 6-month ETDRS score) as the outcome and treatment arm and baseline value of the ETDRS as covariates. Treatment centre was included as a random intercept. The estimated treatment effect is reported as a subject-specific OR (conditional on centre and baseline ETDRS) with 95% CI and corresponding p value. Planned

sensitivity analyses for the primary outcome assessed the impact of missing outcome data and data collected out of window outcome. Linear (Gaussian) mixed regression models were used to analyse continuous secondary outcomes. Binary secondary outcomes were analysed using mixed logistic regression models. For count outcomes, a mixed effect negative binomial model was fitted, which allowed for overdispersion. Pre-planned subgroup analysis investigated whether the treatment effect on the primary outcome differed by retinal detachment, foveal involvement, presence of PVR or retinal incarceration and lens status. For additional details, see online supplemental file 1.

Estimates are presented with 95% CIs and two-sided p values. Statistical analysis was performed using Stata/IC V.15.2 (StataCorp) and a two-sided p value<0.05 was considered statistically significant.

RESULTS

Site recruitment is shown in online supplemental eTable 1. Seven hundred ninety-two patients were screened, 317 were assessed for eligibility and 280 patients were randomised over 75 months. The CONSORT diagram is shown in figure 1. Four patients were withdrawn on the randomisation date from the adjunct group (two patients taking steroids, two were ineligible at the end of surgery). The remaining withdrawals were due to loss to follow-up (seven in each group) or no longer wanting to continue (one from control and two from adjunct group).

Baseline characteristics

Baseline demographics and ocular characteristics are shown in table 1.

Participants were predominantly young white males, with poor preoperative vision (ETDRS zero or worse: 72% control and 78% adjunct) and with just under one-third suffering a Zone 3 injury (21% control and 31% adjunct). Of note, 69% of the control and 77% of the adjunct group had already undergone a primary repair, 48% of the control and 54% of the adjunct group had a pre-existing retinal detachment and PVR was present in 21%–27%, respectively. The time of vitrectomy was a median of 28 (control) and 26 (adjunct) days following the original injury. Operation and follow-up details are shown in table 2.

The groups were similar in terms of surgical gauge, need for lensectomy and silicone oil tamponade. The adjunct group had a higher rate of retinectomy and the follow-up data suggests that there was a higher rate of oil tamponade at both the 3-month and 6-month follow-up visit in the adjunct group.

Primary outcome measure

The proportion of participants with at least a 10-letter improvement in VA over the 6-month post-vitrectomy was 43.4% (n=56/129) in the control group and 46.9% (n=61/130) in the adjunct group (unadjusted difference 3.5% (95% CI −8.6% to 15.6%)) (table 3). The baseline-adjusted OR for clinically meaningful change in VA for the adjunct relative to the control group was 1.03 (95% CI 0.61 to 1.75, p=0.908) indicating no significant difference between the treatment groups. Primary estimand attributes are shown in online supplemental eTable 2. Sensitivity analyses were performed and did not influence the outcome (see online supplemental material 1). Online supplemental eFigure 1 shows the subgroup analyses which suggested that if the fovea was detached, the adjunct increased the odds of an improvement in BCVA (OR 3.46 (95CI 1.16 to 10.36)). However, the 95%CI for this effect overlaps the treatment effect for those with the fovea on, meaning no difference

Table 2 Operation and follow-up details

	Treatment group					
	Control (N=137)		Adjunct (N=143)		Total (N=280)	
Surgeon grade (n, %)						
Consultant	77	56%	95	66%	172	61%
Fellow	60	44%	48	34%	108	39%
Gauge (n, %)						
20G	3	2%	7	5%	10	4%
23G	116	85%	114	80%	230	82%
25G	17	12%	19	13%	36	13%
27G	0	0%	1	1%		
19G endoscope and 23G combined	0	0%	1	1%	1	0%
20G and 23G combined	1	1%	1	1%	2	1%
PVD present (n, %)						
Yes	79	58%	90	63%	169	60%
No	57	42%	53	37%	110	39%
Unknown	1	1%	0	0%	1	0%
Lensectomy (n, %)						
Yes	48	35%	56	39%	104	37%
No	89	65%	87	61%	176	63%
Membrane peel						
Yes	20	15%	23	16%	43	15%
No	117	85%	120	84%	237	85%
Retinectomy (n, %)						
Yes	30	22%	42	29%	72	26%
No	107	78%	101	71%	208	74%
Buckle (n, %)						
Yes	2	1%	3	2%	5	2%
No	135	99%	140	98%	275	98%
Tamponade						
None	24	18%	18	13%	42	15%
Air	18	13%	11	8%	29	10%
SF6	21	15%	24	17%	45	16%
C2F6	1	0%	3	2%	4	1%
C3F8	11	8%	15	10%	26	9%
1300cs SO	32	23%	39	27%	71	25%
5000cs SO	12	9%	13	9%	25	5%
Heavy oil	11	8%	4	3%	15	5%
Other	7	5%	16	11%	23	8%
Complications						
Entry site break	15	11%	11	8%	26	9%
Retinal break	21	15%	20	14%	41	15%
Choroidal haemorrhage	5	4%	10	7%	15	5%
Pre-retinal haemorrhage	11	8%	9	6%	20	7%
AC haemorrhage	7	5%	10	7%	17	6%
Retinal incarceration	4	3%	5	3%	9	3%
Other/unknown	10	8%	18	13%	28	10%
3-Month visit						
Tamponade						
No	76	56%	61	43%	137	49%
Gas	5	4%	0	0%	5	2%
Oil	50	37%	63	44%	113	40%
Unknown	6	4%	19	13%	25	9%
Oil in AC	21	15%	17	11%	38	14%
6-Month visit						
Tamponade						
No	86	63%	73	53%	159	57%
Gas	2	1%	0	0%	2	1%
Oil	38	28%	57	42%	95	34%
Unknown	11	8%	13	9%	24	9%
Interventions during study period 6 months						
Removal of oil	32	23%	26	18%	58	21%

Continued

Table 2 Continued

	Treatment group					
	Control (N=137)		Adjunct (N=143)		Total (N=280)	
Cataract extraction	10	7%	11	8%	21	8%
IOL implantation	17	12%	14	10%	31	11%
Surgical iridotomy	11	8%	13	9%	24	9%
Vitrectomy	30	22%	28	20%	58	21%
Membrane peel	26	19%	36	25%	62	22%
Endolaser	25	18%	27	19%	52	19%
Cryopexy	8	6%	13	9%	21	8%
Tamponade						
Air	3	1%	4	1%	7	7
SF6	2	1%	1	1%	3	3
C3F8	11	8%	23	16%	34	34
1300c SO	8	6%	20	8%	28	28
5000c SO	6	2%	1	1%	7	7
Heavy oil	5	2%	1	1%	6	6
Other	3	1%	4	1%	7	7

AC, anterior chamber; C2F6, hexafluoroethane; C3F8, perfluoropropane; cs, centistokes; G, gauge; IOL, intraocular lens; PVD, posterior vitreous detachment; SF6, sulphur hexafluoride; SO, silicone oil.

in the treatment effect by fovea status cannot be ruled out. There was no difference in outcome in any of the other subgroups including retinal status and fovea status (online supplemental eFigure 1). Sensitivity analyses are shown in online supplemental eTables 3–4 & eFigure 2.

Secondary outcomes analyses

Secondary outcomes are shown in table 3.

For the principle secondary outcome (change in ETDRS VA at 6 months), there was no significant difference between the groups (−2.65, 95%CI −9.22 to 3.92, p value=0.430). There was also no significant difference between the groups for PVR re-detachment, tractional retinal detachment, hypotony, number of operations and quality of life at 6 months. There was a significantly lower rate of stable complete retinal and macular retinal reattachment in the adjunct group compared with the control group (n=65/126, 51.6% adjust vs n=79/123, 64.2% control had complete reattachment and n=68/126, 54.0% adjunct vs n=82/123, 66.7% control had macula reattachment). Elevated IOP was more common in the adjunct group and there was a trend for increased macular pucker, also in the adjunct group.

Adverse events

The summary of the adverse events is shown in figure 2. There was a higher rate of elevated IOP events in the adjunct group compared with the control group (58 vs 45 events, respectively) and a similar rate of hypotony. There were two case of endophthalmitis in the adjunct group. There were six cases of uveitis in the in the adjunct group compared with two in the control group.

DISCUSSION

The ASCOT study is the first large-scale RCT to investigate the use of adjunctive medication to prevent PVR following surgery for penetrating OGT. TA was chosen on the basis of preclinical evidence of its efficacy[13] and promising results from a pilot trial.[8] The primary outcome (improvement in VA) and principal secondary outcome (change in VA) did not demonstrate a significant treatment benefit for TA. The secondary outcome measures failed to show any treatment benefit. The use of combined intraocular and sub-Tenons capsule TA is therefore not recommended as an adjunct to vitrectomy surgery following OGT.

It is notable that stable complete retinal reattachment (51.6% (65/126) TA vs 64.2% (79/123) control group) and stable macular retinal reattachment (54.0% (68/126) TA group vs 66.7% (82/123) control group) at 6 months were significantly worse for the treatment group compared with controls. These two outcomes are related and are clearly of clinical importance. Over a range of baseline parameters, the treatment group appeared to have more severe pathology on presentation. The treatment

Table 3 Outcome data

	Control group	Adjunct group	Difference (adjunct vs control)	OR (adjunct vs control)	P value
Primary outcome					
>10 ETDRS Letter BCVA gain at 6 months	56/129 (43.4%)	61/130 (46.9%)	3.5% (–8.6% to 15.6%)	1.03 (0.61 to 1.75)	0.908
Principle secondary outcome					
Change in ETDRS BCVA at 6 months: mean (SD)	18.9 (29.2)	19.4 (30.8)	–2.65 (–9.22 to 3.92)		
Median (IQR)	5 (0 to 41)	5 (0 to 43)	Adjusted* mean difference		0.430
Secondary outcomes					
Retinal PVR re-detachment	35/124 (28.2%)	42/124 (33.9%)	5.6% (–5.9% to 17.1%)	1.31 (0.76 to 2.27)	0.327
Stable complete retinal reattachment†	79/123 (64.2%)	65/126 (51.6%)	–12.6% (–24.8% to -0.5%)	0.59 (0.36 to 0.99)	0.044
Stable macular retinal reattachment†	82/123 (66.7%)	68/126 (54.0%)	–12.7% (–24.7% to -0.7%)	0.59 (0.35 to 0.98)	0.041
Tractional retinal detachment	30/123 (24.4%)	35/124 (28.2%)	4.5% (–6.7% to 15.6%)	1.22 (0.69 to 2.15)	0.494
Hypotony (within 6 months)‡	28/124 (22.6%)	31/125 (24.8%)	2.2% (–8.3% to 12.8%)	1.13 (0.63 to 2.03)	0.680
Elevated IOP	40/127 (31.5%)	58/125 (46.4%)	14.9% (3.0% to 26.8%)	1.88 (1.13 to 3.15)	0.016
Macular pucker	25/122 (20.5%)	37/124 (29.8%)	9.3% (–1.4% to 20.1%)	1.65 (0.92 to 2.96)	0.093
Number of operations to achieve reattachment	0 (0,0)	0 (0,1)	1.15 (0.68 to 1.94)		0.608
Median (IQR)			Adjusted* incident rate ratio		
VFQ-25 AT 6 months	71.9 (20.9)	72.0 (20.1)	0.78 (–3.53 to 5.10) Adjusted* mean difference		0.723

*Adjusted for centre.
†Without internal tamponade at 6 months.
‡Data taken from secondary outcome form and adverse events form.
ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; PVR, proliferative vitreoretinopathy; VFQ, Visual Function Questionnaire.

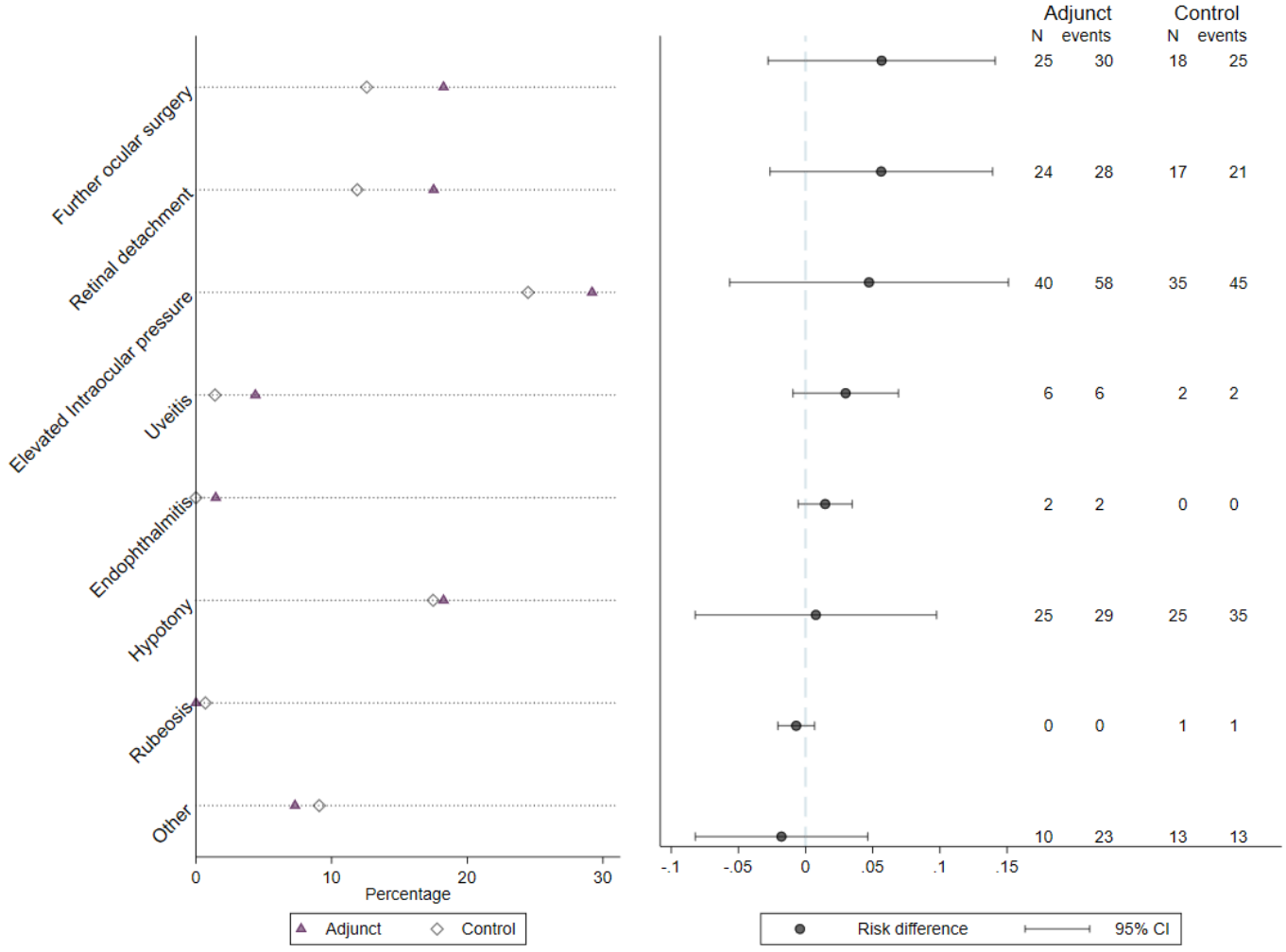

Figure 2 Adverse events. In the control group, other adverse events were: conjunctivitis, graft opacification, swollen disc, vitreous haemorrhage, pupillary membrane, macular oedema, diplopia, total funnel inoperable retinal detachment, focal keratitis, corneal graft failure, corneal oedema, irritation and cystoid macula oedema. In adjunct group, other adverse events were: corneal abrasion, oil in anterior chamber, epiretinal membrane, epiretinal membrane, central macular subretinal bleed, cystoid macular oedema, proliferative vitreo-retinopathy, cataract formation, macular hole, irritation (x2), macular oedema, photophobia (x2), foreign body sensation (x2), pain (x2), watering eye (x2), keratitis at central cornea, intermittent headaches and loose corneal suture.

group, by chance, had a higher level of previous primary repair (77% vs 69%), previous eye surgery (57% vs 49%), zone 3 injuries (31 vs 21%), vitreous haemorrhage (69% vs 63%), retinal incarceration (27% vs 18%), pre-existing retinal detachment (tractional and rhegmatogenous) (54% vs 48%) and pre-existing PVR (27% vs 21%). Although none of these parameters demonstrate a marked difference, taken together they may account for a difference in outcome between the groups. Nevertheless, a negative effect of TA as an adjunct to vitrectomy surgery for OGT cannot be discounted although the pathobiological mechanism for this is unclear. These findings support the conclusion that TA should not be routinely recommended as an adjunct in OGT cases.

Experimental studies have demonstrated that TA has the potential to downregulate the retinal response to injury and reduce the incidence of PVR.[14] The potential for TA to produce a beneficial clinical effect on PVR is supported by pilot and small scale clinical studies suggesting a reduction in the inflammatory response and PVR in retinal detachment and trauma cases.[8 15–17] The reasons for the failure of TA to produce a treatment effect therefore need to be considered. It is possible that in OGT cases where there is extensive blood-ocular barrier breakdown and a markedly upregulated drive towards PVR, the pharmacological effect of TA (at the dosage used in the study) is insufficient to influence the PVR process. In this context, it is notable that a recent uncontrolled study using a stronger antiproliferative agent, mitomycin C at the time of vitrectomy in severe intraocular foreign body cases appeared to reduce the incidence of PVR.[18] Timing of drug delivery will likely have also played a role. Most patients in the ASCOT study had already undergone primary repair of the penetrating injury (69% and 77% of control and adjunct patients) and time of vitrectomy was a median of 28 (control) and 26 (adjunct) days following the primary repair and exceeded 119 days in a quarter of patients (table 1). The use of an adjunctive agent in this subset of patients so long after the original trauma will likely have been too late to alter their outcome or implies that their vitrectomy may not have been directly related their original OGT. Delivery of a therapeutic adjunct at the time of injury, potentially combined with sustained delivery, may produce a greater effect in modifying the PVR process in OGT.

Case selection is an additional factor which may have influenced the results. ASCOT recruited a broad spectrum of open globe trauma cases. Overall, 40% of cases had a globe rupture, 37% penetrating injury, 19% had intraocular foreign bodies and 4% a perforating injury. Cardillo and co-workers[4] documented that these varied injury types have differing incidences of PVR: perforating injuries 43%, globe rupture 21%, penetrating injuries 15% and intraocular foreign bodies 11%. It is likely that the injury subtypes will have differing responses to therapeutic agents and in future studies more focused case selection, potentially limited to only one injury subtype, could result in a positive therapeutic response. Subgroup analysis suggested a possible benefit in eyes in which there was a fovea-involving retinal detachment, although it should be noted that the data was also consistent with no difference and it is well established that subgroup analysis can often be challenging.[19 20] Even so, this subgroup may be of interest in future work.

The results of surgery for PVR have remained unsatisfactory with often poor visual outcomes and a need for multiple procedures. This has led to both preclinical and clinical studies to identify adjunctive agents to modify the disease process and improve surgical results.[21 22] To date, no adjunctive agents have gained widespread acceptance and PVR remains a surgical disease.[14] Intraocular daunomycin[23] and the combination of 5 fluorouracil (5FU) and low-molecular-weight heparin (LMWH)[24–26] have been studied in a series of RCTs. Although these produced promising initial findings—daunomycin reduced re-operations and the 5FU/LMWH combination reduced PVR in high-risk cases—these studies have not resulted in the drugs having widespread use. Likewise, a study of slow-release dexamethasone in established PVR failed to improve anatomical results although macular oedema was reduced and there was a trend to improved VA.[9] A previous study on TA in non-traumatic PVR also failed to show a benefit.[17] The reasons for the failure of these treatments to improve outcomes for PVR surgery is likely multifactorial and appear to relate to a lack of understanding of the PVR disease process and inadequate case selection.

Limitations of the study were its broad inclusion criteria and that it did not specify the indication for vitrectomy. This likely contributed to the observed length of time overall between OGT and vitrectomy in the study (median 27 days (IQR 12–119)). Future PVR trial designs will therefore need to have a clear focus on disease categorisation and the timing of intervention. The use of subconjunctival steroid at the time of the initial primary repair was not recorded as part of the study design, which may have influenced results.

The ASCOT study was designed to investigate TA as an adjunct to vitreoretinal surgery following OGT. It provided a clear answer, in that there was no benefit from TA in a broad mix of OGT cases and adds to the evidence surrounding the treatment of PVR.

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