A randomised controlled trial of adjunctive triamcinolone acetonide in eyes undergoing vitreoretinal surgery for open globe trauma – the ASCOT study

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Scientific summary

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Background

Eyes sustaining penetrating or open globe trauma (OGT) are a group at high risk of severe visual impairment. Retinal detachment (RD) is common in these eyes and multiple surgical interventions are often necessary. Proliferative vitreoretinopathy (PVR) is the most common cause of recurrent RD and visual loss in eyes, with OGT occurring in 10–45% of cases. There is good evidence from experimental, preclinical studies and pilot clinical trials that the use of adjunctive steroid medication, in particular triamcinolone acetonide (TA), can reduce the incidence of PVR and improve outcomes of surgery for OGT.

Objective

The Adjunctive Steroid Combination in Ocular Trauma (ASCOT) study aimed to investigate the clinical effectiveness of adjunctive TA given at the time of vitreoretinal surgery for OGT. This included analysis of the economic and quality of life benefits of the adjunctive treatment. From an NHS perspective, to explore the incremental cost-effectiveness of TA and to explore the cost per quality-adjusted life-year (QALY) of adjunctive TA in vitreoretinal surgery for OGT to determine whether this falls below the National Institute of Health and Care Excellence threshold of £20,000–30,000 per QALY.

Methods

A phase 3 multicentre double-masked randomised controlled clinical trial randomising patients undergoing vitrectomy following OGT to either adjunctive TA (4 mg/0.1 ml into the vitreous cavity and 40 mg/1 ml sub-Tenon's) or standard care. Inclusion criteria were as follows:

1. adult subjects (aged 18 years or over at the time of enrolment)
2. full thickness, open globe ocular trauma undergoing vitrectomy
3. ability to give written informed consent
4. willingness to accept randomisation and attend follow-up for six months.

Patients were recruited prior to vitrectomy surgery and randomised at the completion of surgery. The primary outcome was to determine whether adjunctive intraocular and periocular steroid (TA) improves visual acuity (VA) at six months compared with standard treatment in eyes undergoing vitreoretinal surgery for OGT. This was defined as the proportion of patients with at least 10 letters of improvement in corrected VA on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at six months.

Secondary outcomes were to determine whether adjunctive intraocular and periocular steroid (TA) influences the development of scarring (PVR), RD (stable complete retinal and macular reattachment), intraocular pressure abnormalities and other complications in eyes undergoing surgery for OGT. In addition, to assess the effects of treatment on quality of life measured using the EuroQol Five Dimensions (EQ-5D) questionnaire and the Visual Function Questionnaire-25 (VFQ-25) tools.

The study sample size was calculated from previously published work and two non-randomised trials carried out by the investigators. Based on previous studies, to detect a 19% increase in the proportion of patients with clinically meaningful improvement in VA [from 55% to 74%, corresponding to an odds

ratio (OR) of 2.33], with an allowance for an estimated 7% dropout rate, the target sample size was 300 patients (150 per study arm).

The main analysis followed the intention-to-treat principle and was conducted subgroup blind (i.e. as group A vs. group B) in accordance with the prespecified ASCOT statistical analysis plan. The primary analysis model consisted of a mixed logistic model with change in VA (<10 change in 6-month ETDRS score, ≥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. Linear (Gaussian) mixed regression models were used for the analysis of the principle secondary outcome (change in ETDRS) and other continuous secondary outcomes. Binary secondary outcomes were analysed using mixed logistic regression models.

We conducted a primary cost-effectiveness analysis using VA (≥10-letter improvement in ETDRS score) as the measure of effect, developing incremental cost-effectiveness ratios to express cost-effectiveness in Great British pounds. We conducted a secondary cost-utility analysis using the EQ-5D as the measure of utility to generate a cost per QALY and a cost-effectiveness analysis using vision specific quality of life as the measure of effect. We then compared the generic (EQ-5D) with the visual specific (VFQ-25) measure. Primary and secondary health and social care service use was recorded using a client service receipt inventory as part of a case report form collected at baseline, three and six months.

Results

There were 129 patients in the primary analysis for the standard of care surgery arm and 130 in the surgery plus TA arm. Comparing baseline parameters the treatment group appeared, by chance, to have more severe pathology on presentation – the treatment group had a higher level of previous primary repair – 77% compared with 69%, more zone 3 (posterior) injuries (31% vs. 21%), a higher rate of vitreous haemorrhage (69% vs. 63%) and retinal incarceration (27% vs. 18%) and higher rates of pre-existing RD (54% vs. 48%) and pre-existing PVR (27% vs. 21%). The primary outcome (improvement in VA) and principal secondary outcome (change in VA) did not demonstrate any treatment benefit for TA. A total of 56/129 (43.4%) participants in the standard surgery arm experienced a clinically meaningful improvement in VA (6-month change in ETDRS ≥10 letters) compared with 61/130 (46.9%) in the surgery plus adjunctive TA arm [unadjusted difference in proportion 3.5%, 95% confidence interval (CI) −8.6% to 15.6%]. The adjusted OR for a clinically meaningful change in VA for surgery plus adjunctive TA relative to standard surgery was 1.03 (95% CI 0.61 to 1.75, $p = 0.908$). The baseline adjusted mean difference in the month 6 change in ETDRS VA for surgery plus TA compared with standard surgery was −2.65 (95% CI −9.22 to 3.92, $p = 0.430$), with the point estimate in favour of standard surgery.

Similarly, the secondary outcome measures failed to show any treatment benefit. For two of the secondary outcome measures, stable complete retinal reattachment and stable macular retinal reattachment, outcomes for the treatment group were significantly less good than for the control group. The OR for stable complete retinal reattachment for surgery plus adjunctive TA relative to standard surgery was 0.59 (95% CI 0.36 to 0.99, $p = 0.044$) in favour of standard surgery. The OR for stable macular retinal reattachment for surgery plus adjunctive TA relative to standard surgery was 0.59 (95% CI 0.35 to 0.98, $p = 0.041$) in favour of standard surgery.

For the economic analysis, sample sizes of the intervention arm and control group were 130 and 129, respectively. The cost of the intervention per patient was estimated at £132. The proportion of participants with an ETDRS ≥10-letter improvement was 0.47 for the intervention group, with a mean cost of £4,908, while the control group had a mean cost of £4,794 and an effect of 0.43.

Conclusions

The use of combined intraocular and sub-Tenon's capsule TA is not recommended as an adjunct to vitrectomy surgery for intraocular trauma. Secondary outcome measures suggested a negative effect of the adjunct. The baseline characteristics of the treatment and control groups may provide an explanation for the less good outcomes in the treatment group – the treatment group appeared to have more severe pathology on presentation. A negative treatment effect of the adjunct cannot, however, be discounted.

This is a low-cost intervention; however, it did not produce a significant clinical outcome of effect, and outcome measures did not indicate that it was cost-effective. What is methodologically interesting is that the measurement of preference and non-preference-based outcomes in ophthalmic surgery and VA correlates with generic health-related quality of life measures used for QALY calculation.

Future work

The use of alternative adjunctive medications in cases undergoing surgery for OGT should be investigated. Refinement of clinical grading and case selection will enable better trial design for future studies.

Trial registration

This trial is registered as ISRCTN 30012492, EudraCT number 2014-002193-37, REC 14/LNO/1428, IRAS 156358, Local R&D registration CHAD 1031.

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