Primary trabeculectomy versus primary glaucoma eye drops for newly diagnosed advanced glaucoma: TAGS RCT

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Scientific summary

TAGS RCT

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Scientific summary

Background

Glaucoma is a pressure-related optic neuropathy that results in progressive visual field deterioration. Glaucoma affects ≈ 2% of the UK population aged > 40 years. Glaucoma is the second most common cause of registration as being visually impaired in the UK. In England, there are more than 1 million glaucoma-related visits to the NHS per year. The management of glaucoma patients constitutes a major part of ophthalmologists' workload. The number of people with glaucoma is predicted to increase substantially as the population ages.

Sight loss from glaucoma is preventable. However, people are unaware of the onset of glaucoma because it is typically asymptomatic in the early stages and, as a consequence, in the UK 10–39% of people with glaucoma present with advanced disease in at least one eye. Presentation with advanced visual field loss is the major risk factor for lifetime blindness in people with glaucoma.

Reducing intraocular pressure is currently the only effective treatment for glaucoma. Better control of intraocular pressure from diagnosis reduces the risk of progression to blindness. The primary treatment options in the UK for advanced glaucoma are mainly medical or surgical interventions.

The National Institute for Health and Care Excellence guidelines suggest that patients presenting with advanced disease are offered augmented trabeculectomy as a primary intervention and are offered medical management only if surgery is declined.

Currently, most ophthalmologists treat patients medically with an escalating eye drop regime and are reluctant to carry out primary surgery because of concerns regarding surgical adverse events and an inadequate evidence base to support primary surgery.

By using eye drops as a first-line treatment instead of surgery and by operating only on patients in whom eye drop therapy fails, NHS resources in the short term might be saved. However, the long-term effects on visual outcome and cost are uncertain. Modern glaucoma eye drops lower intraocular pressure significantly better and have fewer side effects than those previously used; therefore, this may reduce the need for surgery.

Avoiding surgery could improve patient health and quality of life. A head-to-head trial of these two primary treatments is, therefore, required.

Objectives

The overarching objectives of this trial are to investigate if eye drop treatment in patients presenting with advanced glaucoma leads to better health-related quality of life than first-line surgery and to determine whether or not this is associated with reduced costs, better clinical outcomes and better safety, and if this is cost-effective.

Primary objective

The primary objective of this trial was to compare primary medical management with primary augmented trabeculectomy (glaucoma surgery) for patients presenting with advanced primary open-angle glaucoma (Hodapp–Parrish–Anderson Classification severe) in terms of patient-reported health status using the National Eye Institute's Visual Function Questionnaire-25.

Secondary objectives

- To compare generic and vision- and glaucoma-specific patient-reported health and patient experiences in the short and medium term.
- To compare the incremental cost per quality-adjusted life-year gained at 2 years of the more effective treatment based on responses to the EQ-5D-5L, the Health Utilities Index and the Glaucoma Utility Index.
- To compare clinical outcomes [i.e. visual field mean deviation changes, logMAR (logarithm of the mean angle of resolution) visual acuity changes, intraocular pressure, Esterman visual field for driving vision and registered visual impairment].
- To compare the need for additional cataract surgery.
- To compare safety by comparing adverse events from both surgical and medical interventions.
- To employ a discrete choice experiment among participants with advanced glaucoma to generate a revised scoring system for the Glaucoma Utility Index that is more sensitive and specific for those with advanced disease.
- To compare lifetime costs and benefits through an economic model.

Methods

Design

We designed a pragmatic, multicentre, randomised controlled trial to compare primary medical management with primary augmented trabeculectomy (standard care). Participants were unmasked to their treatment allocation. Participants were randomised to medical management or primary augmented trabeculectomy (1 : 1 allocation, minimised by centre and bilateral disease). Participants were followed for 2 years and received ongoing care and monitoring in accordance with standard clinical care. Further management decisions were made by the consulting clinician in collaboration with their patient.

Setting

In total, 27 NHS secondary care glaucoma departments, each with at least one fellowship-trained glaucoma specialist, took part in the trial.

Participants

Adult patients with primary open-angle glaucoma (including normal tension, pigment dispersion and pseudoexfoliation glaucoma) presenting with advanced glaucoma in one or both eyes defined as severe according to the Hodapp–Parrish–Anderson classification of visual field loss were eligible to participate in the trial.

Intervention

Primary medical management: escalating medical therapy

Participants randomised to medical management could be prescribed a variety of licensed glaucoma medications (eye drops). These eye drops were used in accordance with National Institute for Health and Care Excellence guidelines. Escalating medical management was defined as follows: study participants may be started on one or more medications at their initial visit depending upon the judgement of the treating clinician. When monotherapy is initiated this should be with a prostaglandin analogue. Subsequent addition of medications was is based on clinician judgement/preference. When drops failed to control IOP adequately oral carbonic anhydrase inhibitors may be used.

Primary augmented trabeculectomy: standard trabeculectomy augmented with mitomycin C

Standard trabeculectomy was defined as the creation of a 'guarded fistula' by making a small hole in the eye, covered by a flap of partial thickness sclera, that allows aqueous humour to egress from the eye into the subconjunctival space. The operation could be performed under either local or general anaesthetic.

The dose of mitomycin C in terms of exposure time and concentration was left to the discretion of the operating surgeon and decided on a case-by-case basis.

Main outcome measures

Primary outcome measure

The primary outcome measure was the score on the vision-specific health profile (Visual Function Questionnaire-25) at 24 months.

Secondary outcome measures

The secondary outcome measures fell into three categories:

1. patient-reported health status – Health Utility Index version 3, EQ-5D-5L, Glaucoma Utility Index, Visual Function Questionnaire-25 and patient experience
2. clinical outcomes – visual field mean deviation, intraocular pressure, logMAR, visual acuity, need for cataract surgery, visual standards for driving, registered visual impairment and safety at 24 months
3. economic outcomes – incremental costs, quality-adjusted life-years, incremental cost per quality-adjusted life-year gained (based on responses to the EQ-5D-5L, Health Utility Index version 3 and updated Glaucoma Utility Index values).

Discrete choice experiment

A discrete choice experiment using the attributes and levels of the Glaucoma Profile Instrument was used to revise the Glaucoma Utility Index scoring system in a population with advanced glaucoma. Trial participants were randomised to one of four blocks, each with 15 choice-set questions. The discrete choice experiment was administered as a postal questionnaire at 27 months post randomisation. Logistic regression methods were used to analyse participants' responses for each choice-set question and quantify the relative importance of each attribute level. The results of the regression analysis were then converted into preference-based weights for the Glaucoma Utility Index.

Economic evaluation

A within-trial analysis was carried out to compare the costs and benefits of medical and surgical management. Resource use was measured using the study case report forms and bespoke questionnaires. Costs were derived from published sources and from study-specific estimates. Missing data were accounted for using multiple imputation. A seemingly unrelated regression was used to assess for the difference between the costs and the EQ-5D-5L, results between treatment arms. Stochastic and deterministic sensitivity analyses were carried out. In addition, a Markov model was used to compare lifetime costs and quality-adjusted life-years between the two treatment arms. The model described disease progression and how treatments may alter that progression. Data for the model came from the Treatment of Advanced Glaucoma Study (TAGS), supplemented with data from the literature. Results were presented as mean costs, mean quality-adjusted life-years and the incremental cost per quality-adjusted life-year gained. The uncertainty surrounding the model findings was assessed using probabilistic sensitivity analysis and deterministic sensitivity analysis.

Results

Between 3 June 2014 and 21 May 2017, we screened 962 potentially eligible patients, of whom 509 were excluded: 233 patients were ineligible and 276 patients declined to participate. We, therefore, recruited 453 participants, of whom 227 were randomised to the trabeculectomy arm and 226 to the medical management arm.

The mean age of the participants was 67 years (standard deviation 12 years) in the trabeculectomy arm and 68 years (standard deviation 12 years) in the medical management arm. More than 65% of participants were male and more than 80% were white. The proportion of patients with bilateral disease was 19.4% in the trabeculectomy arm and 19.5% in the medical management arm. More than 90% of patients had primary open-angle glaucoma and just over 30% had a family history of glaucoma.

At baseline, the mean Visual Function Questionnaire-25 score was 87.1 (standard deviation 13.6) in the trabeculectomy arm and 87.1 (standard deviation 13.4) in the medical management arm; the mean visual field mean deviation (dB) was −14.91 (standard deviation 6.36) and −15.26 (standard deviation 6.34), respectively; and the logMAR visual acuity was 0.15 (standard deviation 0.25) and 0.17 (standard deviation 0.26), respectively. The intraocular pressure was 19.4 mmHg (standard deviation 6.2 mmHg) in the trabeculectomy arm and 19.0 mmHg (standard deviation 5.7 mmHg) in the medical management arm. In total, 27 participants were classified as having sight impairment or severe sight impairment. Other health-related quality-of-life outcomes were balanced between arms.

Twenty-six participants (11.1%) in the trabeculectomy arm did not have surgery. In the medical management arm, 39 participants (17.3%) required trabeculectomy for glaucoma control before the 24-month follow-up.

At 24 months, the difference in the mean Visual Function Questionnaire-25 score between the arms was 1.06 (95% confidence interval −1.32 to 3.43; $p = 0.383$).

The mean difference between arms in EQ-5D-5L score at 24 months was 0.016 (95% confidence interval −0.021 to 0.053; $p = 0.405$). Similarly, the mean difference in Health Utility Index version 3 at 24 months was 0.036 (95% confidence interval −0.006 to 0.078; $p = 0.094$) and the mean difference in Glaucoma Utility Index was 0.011 (95% confidence interval −0.017 to 0.039; $p = 0.434$).

In both arms, participants' perception that their glaucoma was getting worse diminished during the course of the study. At 24 months, there was no evidence of a difference between the treatment arms (relative risk 0.70, 95% confidence interval 0.46 to 1.07; $p = 0.099$).

The mean intraocular pressure at 24 months was 12.40 mmHg in the trabeculectomy arm and 15.07 mmHg in the medical management arm (mean difference −2.75 mmHg, 95% confidence interval −3.84 mmHg to −1.66 mmHg; $p < 0.001$). Fewer types of glaucoma eye drops were required in the trabeculectomy arm than in the medical management arm to achieve this lower intraocular pressure. The logMAR visual acuity at 24 months was slightly better in the medical management arm than in the trabeculectomy arm (mean difference 0.07, 95% confidence interval 0.02 to 0.11; $p = 0.006$). In the case of visual field mean deviation, there was no evidence of a difference between arms at 24 months (mean difference 0.18, 95% confidence interval −0.58 to 0.94; $p = 0.645$).

At 24 months, there was no evidence of a difference between arms in the requirement for cataract surgery (relative risk 0.98, 95% confidence interval 0.50 to 1.95; $p = 0.963$). There was also no evidence of a difference between arms in the number of participants meeting visual standards for driving or registering as sight impaired at 24 months.

The number of participants who had a safety event during the 24-month follow-up was 88 (38.8%) in the trabeculectomy arm and 100 (44.2%) in the medical management arm (relative risk 0.88, 95% confidence interval 0.66 to 1.17; $p = 0.366$). The number of participants who had a serious adverse event was 12 out of 226 (5.3%) for those who received trabeculectomy and 8 out of 226 (3.5%) for those who received medical management.

The logMAR visual acuity declined by > 10 letters in three participants, who were all in the trabeculectomy arm: in two cases because of glaucoma progression and in one case because of a central serous retinopathy. Two participants, one in each arm, developed endophthalmitis.

Discrete choice experiment

Nearly 97% ($n = 438$) of participants who were randomised in the main trial were randomly allocated to a discrete choice experiment block. Of these participants, 70% ($n = 308$) returned the discrete choice experiment questionnaire at least partially completed. Participants reported having a strong preference for improvements in central and near vision, mobility and activities of daily living. Utility values were estimated for all attribute levels and a revised value set for the Glaucoma Utility Index was created and incorporated into the economic evaluation.

Economic evaluation

The within-trial analysis found an increase in average quality-adjusted life-years gained (0.04) and average cost (£2013) in the trabeculectomy arm, giving an incremental cost per quality-adjusted life-year of £45,456. The stochastic sensitivity analysis revealed that the probability of medication being cost-effective is 100% at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year, 88% at the £30,000 threshold and 44% at the £50,000 threshold.

The model-based analysis found that, compared with medical management, trabeculectomy was associated with an average additional cost of £2687, an average additional gain of 0.28 quality-adjusted life-years and an incremental cost per quality-adjusted life-year of £9679 over a patient's lifetime. The likelihood of trabeculectomy being considered cost-effective over a range of society's willingness to pay for a quality-adjusted life-year of £0–20,000 was 73%. The results appeared to be robust over all sensitivity analyses considered.

Conclusions

We found no evidence of a difference in health-related quality of life at 24 months between patients treated with medical management and those treated with surgery. Furthermore, the precision of the confidence intervals shows that any meaningful difference favouring either treatment is incompatible with the data in the Treatment of Advanced Glaucoma Study. Intraocular pressure was better controlled in the trabeculectomy arm, which may have longer-term implications for further visual field progression. It is unlikely that trabeculectomy would be cost-effective over the trial follow-up duration at the range of threshold values for willingness to pay for a quality-adjusted life-year that we considered. However, over a patient's lifetime, the benefits of trabeculectomy, in terms of health-related quality of life, would continue to accrue and the initial costs of surgery would be offset by a reduction in ongoing medication costs. The consequence of these impacts is that, over a patient's lifetime, trabeculectomy is likely to be considered cost-effective over the range of values of society's willingness to pay for a quality-adjusted life-year that we considered.

Implications for health care

The significant additional reduction in intraocular pressure achieved in patients in the trabeculectomy arm decreases the risk of further lifetime visual field loss and vision-related disability. The lack of significant adverse events associated with trabeculectomy will reassure both clinicians and patients of

its safety as a primary intervention, but a judgement is needed by the health service as to whether or not any long-term gains would be worth the extra cost of trabeculectomy.

Recommendations for research

For participants in the Treatment of Advanced Glaucoma Study, longitudinal research into the clinical effectiveness, safety, patient experience and cost of eye drops and trabeculectomy as first-line treatments will determine which treatment offers better lifetime outcomes, specifically:

- the exploration of mechanisms to prevent people presenting with advanced glaucoma
- the development of improved patient-reported outcome measures for measuring glaucoma
- ways to improve clinical trial methodology to reduce the length of time required to undertake a trial for chronic disease
- further research into suitable outcome measures to measure quality of life for glaucoma
- further estimation work to explore the negative preferences reported in the discrete choice experiment
- further research into cross-walking the Visual Function Questionnaire-25 instrument to the EQ-5D-5L to allow comparison between the two measures and to potentially reduce the data collection burden of future trials.

Trial registration

This trial is registered as ISRCTN56878850.

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