Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT

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Scientific summary

The LiGHT RCT

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Scientific summary

Background

Glaucoma is a group of conditions characterised by the progressive damage of the optic nerve head and loss of visual field (VF). It is a leading cause of visual morbidity in the UK, causing falls, road traffic accidents, loss of independence in the elderly and a reduction in quality of life (QoL). Ocular hypertension (OHT), a state of raised intraocular pressure (IOP) in otherwise healthy eyes, is a risk factor for developing glaucoma and often requires treatment. The only known treatment for glaucoma and OHT is lowering the IOP; this has traditionally been done with IOP-lowering eyedrops when patients are treated for the first time.

Glaucoma monitoring and treatment take up a major proportion of hospital eye service outpatient appointments, with > 1 million glaucoma-related hospital eye service visits annually. Glaucoma treatment incurs significant costs to both the NHS and the patients; in 2012 alone, > 8 million glaucoma treatment-related items were dispensed in the community, costing > £105M. In addition, annual increases in the items prescribed and their cost have been reported for more than a decade.

The traditional first-line treatment for glaucoma and OHT, IOP-lowering eyedrops, has numerous side effects both topical and systemic. These range from mild to severe, take up a significant proportion of outpatient visits and may affect the success of further glaucoma surgery. Glaucoma and its treatment have been shown to have a significant negative impact on patients' QoL as a result of impairments in visual function, as well as the side effects of treatment.

An alternative to reducing IOP is selective laser trabeculoplasty (SLT), a quick and painless outpatient procedure. Until now this has principally been used not as a first-line treatment but as a last resort before intraocular surgery. However, this is because earlier forms of laser trabeculoplasty had a relatively low safety margin and repeatability; SLT is better than earlier types of laser trabeculoplasty in both respects.

Selective laser trabeculoplasty has the potential of providing IOP control for glaucoma and OHT patients without the need for topical medical treatment (eyedrops) and this has implications for both NHS expenditure and the patients' QoL. Additionally, the use of SLT from the outset of patients' treatment may offer clinical benefits in the later management of the disease.

Objective

To investigate if lowering IOP with SLT as a first-line treatment for patients with newly diagnosed OHT or open-angle glaucoma (OAG) (Laser-1st) leads to a better health-related quality of life (HRQoL) than first-line treatment with IOP-lowering eyedrops (Medicine-1st), and whether or not this is associated with reduced costs, better clinical outcomes and improved tolerability of treatment.

Objectives

Primary objective

To determine if, in a pragmatic study that mirrors the realities of clinical decision-making, a Laser-1st (initial SLT followed by routine medical treatment) pathway delivers a better HRQoL at 3 years than a Medicine-1st (routine medical treatment only) pathway, in the management of patients with OAG or OHT.

Secondary objectives

To determine whether or not a Laser-1st treatment pathway:

- costs less than the conventional treatment pathway of Medicine-1st
- achieves the desired level of IOP with less intensive treatment over the course of the study
- leads to equivalent levels of visual function after 3 years
- is better tolerated by patients.

Methods

We designed a pragmatic randomised control trial, with participants unmasked to treatment allocation, across six UK NHS sites, to compare initial SLT followed by routine medical treatment (Laser-1st) with routine medical treatment only (Medicine-1st).

Patients were adults, newly diagnosed with OAG or OHT, with no other ocular pathology and were randomised in a 1 : 1 ratio to receive either SLT (Laser-1st) or medical therapy (Medicine-1st). Patients were monitored for 3 years and received care in accordance with standard clinical practice.

Eyes were stratified into predefined categories of disease severity and were treated to achieve an eye-specific target IOP generated by a decision support software (DSS), based on published research and internationally recognised guidelines. SLT was performed in accordance with a strict protocol to standardise energy levels and the number of shots. Medical treatment was conducted and escalated in accordance with guidelines from the National Institute for Health and Care Excellence. Patient care, as well as monitoring intervals and treatment escalations, was guided by the DSS. All DSS suggestions could be overruled by the treating specialist consultant ophthalmologist if this was deemed to be to the patients' benefit. In such cases the consultant was required to record a detailed explanation for the decision. All measurements influencing treatment escalation decisions (VF, Heidelberg retinal tomography and IOP) were made by masked observers.

Patients were sent a series of questionnaires investigating HRQoL, health-care resource use and concordance at 6-month intervals [EuroQol-5 Dimensions, five-level version (EQ-5D-5L), Glaucoma Utility Index (GUI), Glaucoma Symptom Scale (GSS), Glaucoma Quality of Life-15 (GQL-15), a modified Client Service Receipt Inventory and two questions regarding concordance].

Statistical analysis

The primary outcome was analysed using linear regression with terms for randomisation arm, baseline EQ-5D-5L, stratification factors (diagnosis and centre), baseline IOP and number of eyes affected at baseline. The unit of analysis was the patient. If both of a patient's eyes were included, baseline severity and IOP were based on the worse eye, defined using VF mean deviation (MD) at baseline. EQ-5D-5L values missing at 36 months were imputed using values at 30 months, if available. Sensitivity analyses were performed to verify the results of the primary analysis. Mixed-effects models were used to analyse the EQ-5D-5L measurements recorded at all time points to investigate possible changes in treatment effect over the 36 months (using interaction terms between randomisation arm and time) and to estimate the average treatment effect over the 36-month follow-up period. The secondary outcomes were analysed using similar regression methods. All analyses were performed on an intention-to-treat basis with participants analysed according to the arm to which they were randomised.

Economic evaluation

Quality-adjusted life-years (QALYs) were calculated over the course of the trial using the baseline and 6-monthly follow-up EQ-5D-5L questionnaires and calculating the area under the curve. Health-care resource use cost was calculated using published sources. Eyedrops for OAG and OHT were costed based on prescribed medications using the *British National Formulary* [Joint Formulary Committee. *British National Formulary* (online). London: BMJ Group and Pharmaceutical Press. URL: www.medicinescomplete.com (accessed 15 July 2018)]. Cost-effectiveness acceptability curves were generated and the probability that the intervention is cost-effective was investigated for a range of values of willingness to pay.

Results

Between October 2012 and October 2014 a total of 16,379 patients were assessed for eligibility (15,483 were excluded as a result of ineligibility). Of the 896 patients who were eligible, 718 (1235 eyes) were recruited (80.1% participation rate), of whom 356 (613 eyes) were allocated to SLT (Laser-1st pathway) and 362 (622 eyes) to medical treatment (Medicine-1st pathway).

The average age of the patients was 63.1 years (± 11.8 years) and more male patients than females were recruited (55.3% males vs. 44.7% females). In total, 70% of all participants were white (black was the second largest ethnic group; 20%). Thirty per cent of the patients reported a family history of glaucoma affecting at least one first-degree relative.

A total of 301 patients (41.9%) had bilateral OAG, 161 patients (22.4%) had unilateral OAG (fellow eye healthy), 93 patients (13.0%) had OAG in one eye and OHT in the other eye, 124 patients (17.3%) had bilateral OHT and 39 patients (5.4%) had unilateral OHT (fellow eye healthy). A total of 555 patients (77.2%) were classified as having OAG (if at least one eye had OAG) and 163 patients (22.7%) were classified as having OHT; in 517 patients (72.0%) both eyes were eligible for the trial.

At baseline, the average EQ-5D-5L score was similar in the two treatment arms (Medicine-1st 0.92 ± 0.13; Laser-1st 0.91 ± 0.13), as was the GUI score (Medicine-1st 0.89 ± 0.11; Laser-1st 0.89 ± 0.12) and the GQL-15 score (Medicine-1st 18.7 ± 5.6; Laser-1st 18.9 ± 6.6). The average baseline GSS score was slightly higher in the Medicine-1st arm than in the Laser-1st arm (Medicine-1st 83.3 ± 16.6; Laser-1st 81.4 ± 17.2).

Sixteen patients in the Laser-1st arm and nine patients in the Medicine-1st arm withdrew from the trial. A total of 652 patients returned the primary outcome at 36 months, yielding a 91% return rate. At 36 months the Laser-1st arm had an average EQ-5D-5L score of 0.90 [standard deviation (SD) 0.16], compared with 0.89 (SD 0.18) in the Medicine-1st arm [adjusted mean difference (Laser-1st – Medicine-1st) 0.01, 95% confidence interval (CI) –0.01 to 0.03; $p = 0.23$]. Taking into account the outcome data from all time points across 36 months, the two treatment arms had similar EQ-5D-5L scores at 36 months (adjusted mean difference 0.02, 95% CI –0.00 to 0.03).

The Laser-1st arm scored an average of 0.89 (SD 0.13) on the GUI, compared with 0.89 (SD 0.13) for the Medicine-1st arm (adjusted mean difference 0.007, 95% CI –0.010 to 0.025). The Laser-1st arm had a mean GSS score of 83.3 (SD 17.3) at 36 months, compared with 83.1 (SD 17.7) for the Medicine-1st arm (adjusted mean difference 1.595, 95% CI –0.797 to 3.988). The mean GQL-15 scores at 36 months were similar in the two arms (19.8 for Laser-1st and 19.8 Medicine-1st, adjusted mean difference –0.368, 95% CI –0.605 to 1.341).

At 36 months, 536 eyes (87.7%) of 314 patients in the Laser-1st arm and 536 eyes (86.2%) of 306 patients in the Medicine-1st arm were available for analysis of clinical outcomes. The two treatment arms had comparable end-point visual acuity [0.08 (SD 0.17) vs. 0.07 (SD 0.18) log of the minimum angle of resolution,

Medicine-1st and Laser-1st, respectively)], IOP [16.3 (SD 3.9) vs. 16.6 (SD 3.6) mmHg, Medicine-1st and Laser-1st, respectively] and VF MD [–3.2 dB for both arms (SD 3.8 dB Medicine-1st; SD 3.9 dB Laser-1st)].

Overall, 95% of the eyes treated with Laser-1st ($n = 509$) were at target IOP at 36 months, which was achieved without medication for 78.2% of the eyes ($n = 419$), corresponding to 74.2% ($n = 233$, 95% CI 69.3% to 78.6%) of the patients. Of the eyes that received Medicine-1st, 93.1% ($n = 499$) were at target IOP at 36 months; 64.6% ($n = 346$) were using a single medication. During the 36 months of the trial, target IOP was achieved at 93% of visits in the Laser-1st arm, compared with 91.3% of visits in the Medicine-1st arm. The number of treatment escalations was higher in the Medicine-1st arm than in in the Laser-1st arm (348 vs. 299), as was the number of eyes showing disease deterioration (36 vs. 23); 11 eyes in the Medicine-1st arm (1.8%) required IOP-lowering surgery (trabeculectomy), compared with none in the Laser-1st arm. Twenty-five cataract extractions were carried out in the Medicine-1st arm and 13 in the Laser-1st arm.

There were no sight-threatening complications of SLT. The IOP rose > 5 mmHg compared with baseline IOP in six eyes of six patients who received SLT, but only one eye required treatment. Patients in the Medicine-1st arm reported more ophthalmic eyedrop-related adverse events (AEs) (150 aesthetic side effects and ocular allergic reactions were reported by 73 patients) than those in the Laser-1st arm (30 equivalent events were reported by 20 patients). Transient AEs were reported by 34.4% ($n = 122$) of the patients in the Laser-1st arm as a result of the SLT application. AEs during the SLT procedure were reported for 14 patients. Systemic AEs were similar in the two treatment arms. Eyedrop-related systemic AEs were reported more often and by more patients in the Medicine-1st arm than in the Laser-1st arm [148 events reported by 52 patients (14.4%) vs. 87 events reported by 23 patients (6.5%)]. Serious AEs were overall similar in both arms: 95 in the Medicine-1st arm, affecting 68 patients, and 107 in the Laser-1st arm, affecting 64 patients.

Laser-1st dominated Medicine-1st in that it resulted in a greater QALY gain at a lower cost (although the difference was not significant; $p = 0.286$). Laser-1st treatment cost £458 less than Medicine-1st, with 95% of bootstrap iterations falling between –£585 and –£345 (for specialist eye-related costs), and had a mean incremental QALY gain of 0.011, with 95% bootstrap iterations falling between –0.024 and 0.050. Over 36 months, discounted and adjusted, at willingness to pay for a QALY of £20,000 and £30,000, the probability that Laser-1st is more cost-effective than Medicine-1st when only ophthalmology costs are included is 97% and 93%, respectively. When community- and non-eye-related costs are added, there is a 68% chance that Laser-1st is more cost-effective, at willingness-to-pay levels of both £20,000 and £30,000.

Conclusions

This study shows that patients newly diagnosed with glaucoma or OHT can be safely treated with SLT and achieve predominantly eyedrop-free IOP control over at least 3 years, with less intense treatment, fewer AEs and a reduced need for glaucoma and cataract surgery, than patients treated with IOP-lowering eyedrops. This can be achieved at a lower cost per QALY than standard medical therapy alone and with a similar effect on generic HRQoL as assessed by the EQ-5D-5L. Primary SLT is a cost-effective alternative to eyedrops that can be offered to patients with OAG or OHT who need IOP-lowering treatment.

Implications for health care

The findings of this trial have the potential to change glaucoma and OHT treatment worldwide. An eyedrop-free IOP control may be a desired form of treatment for many patients and clinicians, while also providing a cost-effective alternative to eyedrops. The results of this study may also have important implications for resource-poor health-care settings where access to medication is a major barrier to glaucoma treatment and/or where glaucoma prevalence is high.

Despite the promising results with regard to the safety of the SLT procedure and the eyedrop-free IOP control that SLT offers, clinicians need to consider the perceived necessity of monitoring visits by the patient (patients may not always comprehend the necessity of frequent monitoring) in the absence of daily medication. Patients need to understand the importance of attending follow-up visits and the lifelong need for monitoring. SLT should not be perceived as a one-off glaucoma or OHT treatment and this needs to be communicated clearly to patients.

Recommendations for research

- Longitudinal research into the clinical efficacy of SLT as a first-line treatment, with particular focus on disease progression and ocular surgery rates.
- Longitudinal research into the effect of SLT on subsequent medicine-taking behaviour.
- Longitudinal HRQoL in OAG and OHT in particular (where data are lacking) to understand the impact of medical treatment on patients over a longer period of time, when more intense medical treatment might become necessary.

Longer follow-up already under way (the Laser in Glaucoma And Ocular Hypertension extension trial) will help us answer the majority of the above questions.

Trial registration

The trial is registered as ISRCTN32038223.

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