NICE National Institute for Health and Care Excellence

2019 exceptional surveillance of glaucoma: diagnosis and management (NICE guideline NG81)

Surveillance report

Published: 12 September 2019

www.nice.org.uk

Contents

Surveillance decision 3

Reasons for the decision 3

Overall decision 11

How we made the decision 12

Evidence 12

Views of stakeholders 12

Surveillance decision

We will update the guideline on glaucoma: diagnosis and management.

Reasons for the decision

Assessing the evidence

The purpose of this exceptional review was to examine any impact on the NICE guideline following the publication of a Health Technology Assessment (HTA) report on Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT (Gazzard et al. 2019). No additional evidence published since the NICE guideline launched in November 2017 was considered by the exceptional review.

HTA review summary

Methods

The randomised controlled trial (RCT) assessed the effectiveness and cost-effectiveness of selective laser trabeculoplasty (SLT) compared with eye drop medication in treatment-naive patients who had open angle glaucoma (OAG) or ocular hypertension (OHT) in 1 or both eyes, which a glaucoma specialist consultant ophthalmologist determined needed treatment. Adult patients (at least 18 years old) newly diagnosed with OAG (n=555) or OHT (n=163) in 6 UK hospitals were randomly allocated to receive either eye drops (n=362) or SLT (n=356) as first-line treatment.

Exclusion criteria included any signs of advanced glaucoma, secondary glaucoma or any angle closure, any contraindication to SLT or an inability to use topical medical therapy, any previous treatment for OAG or OHT.

Patients were monitored for 3 years, with routine follow-up appointments based on disease severity and lifetime risk of loss of vision, in line with the NICE guideline; and monitoring periods could be adjusted according to a defined protocol which considered intraocular pressure (IOP) control, disease progression or adverse reactions.

Patients and clinicians were aware of the treatment, but observers that undertook the clinical measurements were blind to the treatment allocation; and treatment, follow-up and treatment escalation decisions were masked by using a computerised evidence-based decision support algorithm.

In the eye drop group, medication provided to patients followed the recommendations in the NICE guideline, with first-line medication being a prostaglandin analogue (PGA); second line, a beta-blocker (once in the morning or in a PGA combination); third or fourth line, a topical carbonic anhydrase inhibitor or alpha-adrenoceptor agonist. Surgery was offered once maximum treatment intensity ('the most intensive combination of eye drops a given individual can reasonably, reliably and safely use') was reached.

In the SLT group, if after 2 SLT treatments further treatment escalation was required, patients were put on eye drop medication and followed the protocol for the eye drops arm. If there were significant complications of laser treatment, or other new medical conditions occurred (e.g. a new history of uveitis or rubeosis) further treatment with SLT was contraindicated.

An objective treatment IOP target was set for each eye (by the computerised decision algorithm), with the lowest possible target of 8 mmHg for OAG and 18 mmHg for OHT.

The primary outcome measure of interest was health-related quality of life (HRQoL) measured using EQ-5D-5L utility scores at 3 years.

The secondary outcomes measures included:

- Glaucoma-specific treatment-related quality of life measured using the Glaucoma Utility Index (GUI).
- Treatment pathway UK healthcare resource use, cost and cost-effectiveness.
- Patient-reported disease and treatment-related symptoms using the Glaucoma Symptom Scale (GSS); patient-reported visual function using the Glaucoma Quality of Life-15 (GQL-15) questionnaire; measurements of IOP-lowering and visual function preservation (e.g. treatment intensity and time taken to achieve target IOP, the number of target IOP revisions, proportion of patients achieving target after each year of treatment, number of patients with confirmed disease deterioration and rates of ocular surgery).

- Safety measures.
- Treatment concordance (Gazzard et al. 2019).

Results

Quality of life

An intention-to-treat analysis indicates that at 3 years follow-up there was no difference in quality of life (EQ-5D-5L) between patients with OAG or OHT receiving as first-line treatment either eye drops (data available from n=323 of 362 patients allocated to eye drops) or SLT (n=329/356). The adjusted mean difference between SLT and eye drops was 0.01 (95% confidence interval [CI] –0.01 to 0.03; p=0.23).

It should be noted that the original sample size for the study (n=718) was chosen as this reflects the number of 'participants required to detect a difference of 0.05 in EQ-5D-5L between the 2 arms at 36 months using a two-sample t-test at the 5% significance level, with 90% power, assuming a common standard deviation of 0.1982 and a 15% loss to follow-up' (for example n=610; Gazzard et al. 2019).

For glaucoma-specific HRQoL tools, there were no significant differences between treatments when comparing scores at 3 years for GUI, GSS score or mean GQL-15 scores. When these outcomes were analysed at 6-monthly intervals, a repeated-measures analysis showed that GSS scores were worse in the eye drop condition at 5 out of 6 time points over 36 months, indicating that there may be some quality of life benefits to SLT over eye drops.

Clinical outcomes

For clinical outcomes, at 3 years follow-up there was no difference found in visual function between the SLT (n=314) and eye drops (n=312) groups, with both groups achieving reduced IOP levels compared to baseline, regardless of severity of condition (OHT, mild, moderate or severe OAG). There were also no differences between the groups in achieving target IOP: target IOP was achieved at the first planned visit in 91.0% of patients in the SLT group and 89.6% in the eye drops group; and in 93.0% of visits in SLT group compared with 91.3% of visits in the eye drops group over the 3 years. The percentage of eyes at target IOP at 12 months was 94.7% (SLT) compared with 96.2% (eye drops) and 95.0% (SLT) compared with 93.1% (eye drops) at 3 years. In relation to the intensity of treatment

required to achieve target IOP, primary SLT gave eye drop-free IOP control for at least 3 years to 74.2% of patients (78.2% of eyes treated). In the eye drop group, 64.6% of eyes achieved target IOP with only a single eye drop medication. Visual field mean deviation and visual field pattern standard deviation were similar in both groups at 3 years.

Adverse events

On average, 3 adverse events (AEs) were reported per patient in the SLT group (total AEs 900) and 4 AEs per patient in the eye drop group (total AEs 1,196), but the number of patients reporting at least 1 AE was similar (261 versus 260, SLT versus eye drops). The authors of the RCT noted that there was a lower rate of SLT-related AEs than has been previously reported. The number of systemic AEs reported by patients in the SLT and eye drops group was similar (236 in 98 patients versus 298 in 115 patients) but differed for drug-related AEs such as tiredness and taste disturbances (87 in 23 SLT patients versus 148 in 52 eye drop patients) and ophthalmic AEs such as aesthetic eye drop side effects, periocular pigmentation or excessive lash growth (492 in 188 patients versus 809 in 241 patients). The number of serious AEs reported was similar between groups (eye drop group: 97 AEs reported by 69 patients; SLT: 107 AEs reported by 64 patients).

The trial also reported that patients in the SLT group were less likely to require cataract surgery than those in the eye drop group (13 eyes versus 25 eyes); and none in the SLT group needed any glaucoma surgery in the first 3 years, whereas 11 patients in the eye drop group did require glaucoma surgery.

Treatment concordance

Overall treatment concordance was good. While the proportion of patients who reported taking eye drops correctly was initially lower in the eye drops group compared to the (small number of participants) in the SLT group who used eye drops (75.0% versus 92.5% concordance respectively), at 3 years self-reported concordance was at 99% in both groups.

Health and social care costs and cost-effectiveness

The total adjusted and discounted health and social care costs for the SLT treatment arm over 3 years is reported to be £3,890 (SE £245; 95% CI £3,409 to £4,371) and for eye drops treatment arm is £3,993 (SE £215; 95% CI £3,571 to £4,414), which is a non-significant difference of –£103 between SLT and eye drops (SE £325; 95% CI –£739 to

£534; p=0.752). When imputed missing community data is included there remains a non-significant difference in costs of –£105 (SE £348; 95% CI –£788 to £579; p=0.764).

SLT as first-line treatment was reported to result in (non-significantly) more quality-adjusted life years (QALYs) at a lower cost than eye drops. The cost-effectiveness analysis reported that at a willingness to pay of £20,000 to £30,000 per QALY gained, SLT is likely to be more cost-effective than eye drops as a first-line treatment when either ophthalmology-only costs are included, or when community and non-eye related costs are also included.

The authors of the study concluded that SLT 'is an efficient, safe and cheaper alternative to eye drops' and should be considered as a first-line treatment for OAG and OHT in need of IOP reduction.

Guideline development

The evidence which informed recommendations 1.5.16 and 1.5.18 to 1.5.20 on the use of laser trabeculoplasty as a treatment for OHT or chronic open angle glaucoma (COAG) in the NICE guideline is from the evidence review undertaken for the original NICE guideline on glaucoma, which published in 2009. This included a systematic search for RCTs which assessed the effectiveness and/or cost-effectiveness of laser trabeculoplasty treatment compared to pharmacological treatments alone or laser and pharmacological treatments combined compared to pharmacological treatments in COAG patients. Searches were from database inception date to 4 August 2008.

Laser trabeculoplasty treatment compared with pharmacological treatments alone

Three RCTs were identified (Migdal et al. 1994, Gandolfi et al. 2005 and Nagar et al. 2005). These were supplemented with relevant data from a Cochrane systematic review (Rolim et al. 2007).

A meta-analysis indicated that there was no statistically significant difference between laser trabeculoplasty and pharmacological treatment in terms of number of patients with an unacceptable IOP at 2 to 48 months follow-up. The evidence was assessed using GRADE as very low quality.

The studies did not report on the other outcomes of interest: mean change in IOP from

baseline (expressed as an absolute value with standard deviation), and number of patients with visual field progression.

No cost-effectiveness studies that met the inclusion criteria were identified which compared laser trabeculoplasty to pharmacological treatment.

It should be noted that only 1 RCT (Nagar et al. 2005) investigated the effectiveness of SLT, while the other 2 RCTs (Migdal et al. 1994 and Gandolfi et al. 2005) investigated the effectiveness of argon laser trabeculoplasty (ALT). While SLT is similar to ALT, it uses a different laser with a discharge of a very short duration. The spot size of the laser beam is much larger than that used for ALT so accurate identification of the trabecular meshwork is not as critical and the procedure is technically simpler. The mechanism of action is thought to be the same as ALT, but re-treatments are said to be less likely to cause raised IOP because there is less photocoagulative damage to adjacent tissue. SLT has now superseded ALT, as it has been found to be associated with 'fewer adverse events, greater ease of use, and improved reliability' (Gazzard et al. 2019).

Laser trabeculoplasty plus pharmacological treatment versus pharmacological treatment

Two RCTs were identified (Sherwood et al. 1987 and Moriarty et al. 1988) which were also supplemented with relevant data from the Cochrane systematic review (Rolim et al. 2007). Both studies assessed only ALT. A meta-analysis indicated that there was no statistically significant difference between laser trabeculoplasty with pharmacological treatment versus pharmacological treatment alone in terms of number of patients with an unacceptable IOP at 12 months follow-up. The evidence was assessed as very low quality.

Recommendation for research

The original NICE guideline from 2009 reported that the comparative effectiveness and cost-effectiveness of laser treatment compared with PGAs was unknown due the lack of evidence, and because existing trials of laser trabeculoplasty were using outdated pharmacological agents in the comparison groups. The role of laser trabeculoplasty in COAG management could therefore not be clearly defined and it was agreed that further research was 'essential to inform future updates of key recommendations in the guideline'.

The following research question was developed: 'What is the effectiveness and cost-effectiveness of initial argon, diode or selective laser trabeculoplasty treatment compared

to PGA alone or laser + PGA in combination in COAG patients?'

The need for further research in this area was also highlighted in the Cochrane review (Rolim et al. 2007).

The effectiveness of laser procedures in reducing IOP was not an area considered in the development of the latest NICE guideline as a surveillance review in 2015 found only 1 relevant RCT which had a small sample size, differing baseline IOP values between treatment groups, and did not include sham laser treatment.

Views of topic experts

In this exceptional review we engaged with topic experts who were members of the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We received responses from 4 topic experts, all of whom felt the guideline should be updated. The topic experts were an academic specialising in glaucoma studies and ophthalmic epidemiology, a consultant optometrist, and 2 optometrists.

The responses from the topic experts suggested that, based on the effectiveness and cost-effectiveness findings from the study, they thought that patients newly diagnosed with OHT or COAG should be offered SLT as a first-line option.

Topic experts were also asked about usual UK practice concerning the use of eye drops or SLT for treating adult patients with OHT or COAG. They responded that it is usual practice for all patients requiring eye pressure lowering (OHT or COAG) to be offered eye drops as first-line treatment; that SLT is not widely offered as a first-line treatment option, it is usually offered later on in the course of disease, after 1 to 4 medications have been tried; but those with advanced vision loss due to COAG may be offered SLT as a first-line treatment option 'although it is rare to have to consider trabeculectomy as a first-line treatment option'. It was reported that SLT is available in the majority of centres, so many would not need to purchase additional equipment, but it was also noted that there may be a 'considerable resourcing issue' in relation to an increase in laser procedures and in the probable need to upskill some non-medics to support the delivery of SLT. In relation to the latter issue, 1 topic expert said that research on enablers and barriers to implementation of non-medical input for glaucoma related laser procedures is necessary to support any recommendation that SLT is offered as a first-line treatment.

Impact

The HTA report findings are directly relevant to recommendations on the treatment of OHT (recommendations 1.5.3 to 1.5.8) and COAG (recommendations 1.5.12 to 1.5.20) in the NICE guideline. For the treatment of OHT:

- The recommended first-line treatment is PGA eye drops, followed by consideration of a beta-blocker if PGAs cannot be tolerated, then non-generic PGA, carbonic anhydrase inhibitors, sympathomimetics, miotics or a combination of treatments.
- For those whose current PGA treatment is not reducing IOP sufficiently to prevent the risk of progression to sight loss, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic drugs should be offered.
- There are no recommendations concerning the use of SLT as a treatment for OHT, but recommendation 1.5.7 says to 'refer people whose IOP cannot be reduced sufficiently with pharmacological treatment to prevent the risk of progression to sight loss to a consultant ophthalmologist to discuss other options'.

For the treatment of COAG:

- Offer a generic PGA to people with COAG (recommendation 1.5.12).
- Offer people with advanced COAG, surgery with pharmacological augmentation (MMC) as indicated (recommendation 1.5.13).
- In people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss despite pharmacological treatment, laser trabeculoplasty can be offered.
- For people with COAG who cannot tolerate a treatment, drugs from another therapeutic class or preservative-free eye drops (if evidence of allergy) should be offered, and laser trabeculoplasty is only recommended as a consideration 'after trying drugs from 2 therapeutic classes', with MMC also recommended (recommendation 1.5.18).
- If someone with COAG has not had a sufficient reduction in IOP following surgery, it is recommended that laser trabeculoplasty can be offered (or pharmacological treatment, further surgery, or cyclodiode laser treatment).

- And for people with COAG who prefer not to have surgery/surgery is not suitable, it is recommended that they are offered pharmacological treatment, laser trabeculoplasty or cyclodiode laser treatment.

The new RCT evidence indicates that SLT is equally effective as eye drops as a first-line treatment for glaucoma or OHT in relation to quality of life and clinical outcomes (including visual field progression and achieving target IOP); and the cost-effectiveness analysis indicates that, compared to eye drops as a first-line treatment, SLT as a first-line treatment results in more QALYs for a lower cost. SLT is likely to be cost-effective at a willingness to pay of £20,000 to £30,000 per QALY.

The RCT addresses the recommendation for research highlighted as of high importance in the original NICE guideline. It was undertaken within the UK, provides UK health and social care costs, and has a large sample size. While it has some limitations (for example, it did not include sham laser treatment and was a single-blind trial as patients were inevitably aware of the treatment they received), it was designed to follow pragmatic clinical practice by ensuring treatments were appropriately tailored to the clinical needs of each patient, which provides a good understanding of the real world application, effectiveness and cost-effectiveness of SLT as a first-line treatment for glaucoma and OHT.

After considering the new evidence and views of topic experts, we have concluded that there is an impact on the recommendations within the NICE guideline. For this reason, we will update it.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering the impact of the evidence on current recommendations, we decided an update is necessary.

See how we made the decision for further information.

How we made the decision

Exceptionally, significant new evidence may mean an update of a guideline is agreed before the next scheduled check of the need for an update. The evidence might be a single piece of evidence, an accumulation of evidence or other published NICE guidance.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence

This surveillance report provides an overview of a randomised controlled trial (RCT) published since the launch of the NICE guideline in 2017. The results of this RCT, alongside topic expert feedback, were considered in detail to determine if there was an impact on the recommendations within the NICE guideline.

Views of stakeholders

Because this was an exceptional surveillance review, we did not consult on the decision.

ISBN: 978-1-4731-3545-1