An external pilot study to test the feasibility of a randomised controlled trial comparing eye muscle surgery against active monitoring for childhood intermittent exotropia [X(T)]

Michael Clarke,[1,2*] Vanessa Hogan,[3] Deborah Buck,[2] Jing Shen,[4] Christine Powell,[1] Chris Speed,[3] Peter Tiffin,[5] John Sloper,[6] Robert Taylor,[7] Mahmoud Nassar,[8] Kerry Joyce,[4] Fiona Beyer,[4] Richard Thomson,[4] Luke Vale,[4] Elaine McColl[3] and Nick Steen[4]

[1]Department of Ophthalmology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK
[2]Institute of Neuroscience, Newcastle University, Newcastle, UK
[3]Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, Newcastle, UK
[4]Institute of Health and Society, Newcastle University, Newcastle, UK
[5]Sunderland Eye Infirmary, City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK
[6]Moorfields Eye Hospital NHS Foundation Trust, London, UK
[7]Department of Ophthalmology, York Hospitals NHS Foundation Trust, York, UK
[8]Ophthalmology Department, Faculty of Medicine, Minia University, Al-Mini, Egypt

*Corresponding author

Declared competing interests of authors: Elaine McColl received grants from Newcastle University, fees and expenses from the NIHR Journals Library Editorial Board and expenses for meeting attendance from the National Institute for Health Research (NIHR) Programme Grants for Applied Research (PGfAR) panel during the course of the study. Luke Vale is a member of the NIHR PGfAR and the NIHR Health Technology Assessment (HTA) Clinical Evaluation and Trials Board.

Published May 2015
DOI: 10.3310/hta19390

Scientific summary

Monitoring for childhood intermittent distance exotropia

Health Technology Assessment 2015; Vol. 19: No. 39
DOI: 10.3310/hta19390

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Strabismus, also known as squint, is an ophthalmic condition in which the eyes are misaligned and therefore look in different directions, i.e. one eye looks straight ahead while the other turns either outwards (exotropia), inwards (esotropia), upwards (hypertropia) or downwards (hypotropia). It may be constant (with loss of binocular function) or intermittent (with binocular function when the squint is not present). Squint can occur in children or adults and may have functional, aesthetic and psychosocial consequences. For example, teenagers and adults with squint have reported problems with self-esteem, self-image and interpersonal relationships, have met ridicule at school or work, and may attempt to avoid activities that bring attention to their condition or to develop strategies that conceal it. Similarly in young children, squint has been linked to lower psychosocial functioning, poorer interpersonal relationships and lower self-esteem. It has been shown that children as young as 5 years of age are significantly more likely to have negative social reactions to peers with strabismus, and that teachers rate photographs of children with strabismus more negatively than those with straight eyes.

Intermittent exotropia [X(T)] is one of the commonest types of childhood strabismus. In this condition, one eye intermittently drifts outwards. It is possible for X(T) to develop into a constant squint [constant exotropia (XT)], potentially leading to loss of stereo vision and/or the development of amblyopia (reduced acuity in one eye caused by decreased quality visual input during the critical period of development). Typically, X(T) is first spotted in early childhood by parents noticing that their child's eye is wandering outwards as they look at objects in the distance, or when they are very tired, inattentive or in bright sunlight.

Conservative treatment options for X(T) include occlusion with eye patches or wearing glasses that stimulate convergence. Eye muscle surgery can also be performed in order to realign the eyes. However, many clinicians and parents opt for an active monitoring approach, i.e. they decide to wait and see whether the squint resolves spontaneously or at the very least does not deteriorate. Long-term natural history data are lacking, but there is some indication from observational work that X(T) surgery is more successful than conservative treatment and active monitoring in improving control of the eyes. However, the success of surgery is not guaranteed and comes with risks.

The lack of trial-based evidence means that the true effectiveness of treatment in ameliorating or curing the condition is unknown. Moreover, even when surgery is the preferred course of action there is little agreement on whether or not immediate surgery is more effective than delaying the operation for a specified length of time or until a certain age.

The current investigators hope to conduct such a trial, if feasible. As the recruitment phase in any trial is one of the most challenging, and given the potential recruitment barriers that are particularly inherent in paediatric or surgical trials, we are first undertaking the SamExo (Surgery vs. Active Monitoring in Intermittent Exotropia) pilot trial in order to assess feasibility and inform the design and conduct of a full-scale trial.

Objectives

The specific objectives of the SamExo pilot trial were to:

1. determine whether or not participating centres were likely to recruit a sufficient number of patients to deliver a full trial
2. determine whether or not recruited patients would stay within their allocated groups and complete follow-up in sufficient numbers to deliver the trial
3. identify reasons why parents accepted or declined participation in the trial
4. pilot the procedures involved in the trial including recruitment (giving information and obtaining consent), randomisation, intervention (surgery), masking, outcome measurements, and web-based trial management and data capture systems.

Methods

Design

The SamExo trial was a rehearsal pilot randomised controlled trial (RCT) to assess the feasibility of a full RCT of the effectiveness of surgical treatment against active monitoring in X(T).

Setting

Four secondary ophthalmology care facilities at The Newcastle upon Tyne Hospitals UK NHS Foundation Trust (co-ordinating site), Sunderland Eye Infirmary, Moorfields Eye Hospital and York NHS Trust, each of which are large centres with specialist paediatric ophthalmology clinics.

Participants

Children aged between 6 months and 16 years, with suspected X(T), who were referred to the clinics from community screening, general practice or other health-care professionals, and subsequently diagnosed with X(T), as well as existing patients fulfilling the eligibility criteria.

Interventions

Clinic appointments

The assessments involved routine clinical measurements together with the evaluation of quality of life (QoL) using the Intermittent Exotropia Questionnaire and collection of associated costs using a Health Services Use Questionnaire, and a Time and Travel Costs Questionnaire. Children in the active monitoring group were offered surgery if a constant strabismus appeared to be developing or parents requested surgery and the responsible clinical team agreed that this was appropriate.

Eye muscle surgery

Surgery was performed by the local Principal Investigator, or delegated deputy, in accordance with agreed surgical formulae tailored to the clinical characteristics of the strabismus and the usual practice of the surgeon. Principles involved in the surgical treatment of children in the study were agreed as follows:

- general anaesthesia
- bilateral lateral rectus recession surgery to be performed for true distance exotropia
- unilateral recess/resect surgery to be performed for other types of exotropia
- standard sterile preparation of the operative site
- conjunctival incisions
- standard isolation and cleaning of muscle to be operated
- muscle secured with 6/0 VICRYL® (polyglactin 910) suture (Johnson & Johnson, New Brunswick, NJ, USA)

- amount of recession/resection assessed on the basis of the maximum distance angle according to table, modified according to standard practice of surgeon
- measurement of amount of muscle adjustment to be checked post placement of scleral sutures
- conjunctival incisions closed with VICRYL sutures
- topical anaesthetic and antibiotic drops given at end of procedure.

Surgical technique was carefully recorded and monitored during the pilot with a view to standardising surgical technique, as far as it was possible to do so.

Outcome measures

The key outcomes of this pilot study were:

- data on the variability of the primary and secondary outcome measures
- rates of participant recruitment and randomisation
- nature and extent of participation bias
- rates of crossover and retention of recruited participants
- nature and extent of biases arising from crossover or loss to follow-up.

Secondary outcomes include age-specific QoL assessments, median scores of control of exotropia assessed by parental report and clinical components of the Newcastle Control Score (NCS) and the Mayo Score and rates of amblyopia. Economic outcomes were restricted to the completion rates of data collection tools. No formal economic analysis was conducted.

Results

All sites that began recruitment of patients were retained throughout the Pilot Rehearsal Trial and all have expressed an interest in continuing with a full trial.

Patient retention rate was also high, with 47 of 49 (96%) of recruited participants attending the final appointment, scheduled at 9 months post randomisation.

In total, 231 children were screened (expected 240), 138 (60%) of whom were eligible (expected 228: 95%) and 49 (35% of eligible) children were recruited (expected 144: 64% of eligible). Many more children than predicted did not fulfil the eligibility criteria for the study (10/240 predicted vs. 93/231 observed). Reasons for non-eligibility were determined for 87 of 93 (94%). The most common reason for children not to meet the eligibility criteria was that their strabismus was not sufficiently severe.

Consent was obtained from 56 of 89 (63%) 'eligible not recruited' (ENR) patients to record baseline and 9-month follow-up clinical data. The demographic and clinical characteristics of the ENR group were compared with those who agreed participation in SamExo. Those who agreed to take part had poorer control of their exotropia (as assessed by the NCS) than those who declined; although statistically significant, this difference is unlikely to be clinically significant.

Conclusions

We have demonstrated that it is possible to recruit and retain participants to a trial of surgery compared with active monitoring for X(T); however, despite screening the anticipated number of children with X(T), recruitment levels fell short of those predicted. This can be attributed to two issues.

First, the proportion of children eligible for inclusion was much lower than anticipated. This was primarily due to the proportion of screened children who did not have a severe enough strabismus for inclusion. Tightening the inclusion criteria to conform with current clinical practice would, while reducing the number of potential recruits overall, increase the proportion who were eligible.

Second, given the expressed views of many parents of children who were eligible for inclusion regarding their preferences – both for and against surgical treatment for X(T) – the development of a formal RCT should include consideration of a preference arm, which would increase the participation of eligible children.

Although not powered to assess the effectiveness of surgery as an intervention, the clinical outcomes do indicate agreement with previous research which suggests that, over a short follow-up period, the majority of patients who are actively monitored do not significantly improve or deteriorate, whereas most patients who undergo surgery have, in the short term, improved alignment, albeit with a rate of between 10% and 20% of overcorrection with a deterioration in stereoacuity.

Trial registration

This trial is registered as ISRCTN44114892.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 09/01/20. The contractual start date was in January 2011. The draft report began editorial review in July 2013 and was accepted for publication in January 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).