Ab interno trabecular bypass surgery with Schlemm’s Canal Microstent (Hydrus) for open angle glaucoma (Protocol)

Otarola F, Hu K, Gazzard G, Bunce C
Ab interno trabecular bypass surgery with Schlemm’s Canal Microstent (Hydrus) for open angle glaucoma

Francisco Otarola¹, Kuang Hu², Gus Gazzard², Catey Bunce³

¹Glaucoma, Moorfields Eye Hospital NHS Foundation Trust, London, UK. ²Moorfields Eye Hospital NHS Foundation Trust, London, UK. ³Department of Primary Care & Public Health Sciences, Kings College London, London, UK

Contact address: Francisco Otarola, Glaucoma, Moorfields Eye Hospital NHS Foundation Trust, 162 City Road, London, EC1V 2PD, UK. fjotarola@gmail.com

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The main objective is to assess the results at two years of ab interno trabecular bypass surgery with Hydrus for OAG in comparison to conventional medical, laser, or surgical treatment in terms of efficacy and safety. A secondary objective will be to examine the effects of Hydrus surgery in people who have concomitant phacoemulsification in comparison to those who do not have concomitant phacoemulsification.

BACKGROUND

Description of the condition

Glaucoma is a chronic progressive optic neuropathy, affecting up to 4% of people by the age of 80 years (Burr 2007). It is the leading cause of irreversible blindness, affecting 60 million people globally (Quigley 2006). This figure is expected to increase to 80 million people by 2020. Open angle glaucoma (OAG) is the commonest type, accounting for three-quarters of cases (Quigley 2006). In one large population cohort, one in six patients with OAG became bilaterally blind (Peters 2013). The only proven way to prevent vision loss is to reduce the pressure inside the eye (intraocular pressure) over the long term (AGIS 2000; CNTG Study Group 1998; Heijl 2002; Kass 2002). Approaches to reducing intraocular pressure (IOP) include medical therapy, laser treatments, and surgery. Because commercially available eye-drop preparations have a short-lasting effect, medical therapy requires eye-drops to be instilled one or more times daily for life. Adherence is very poor, even if use is monitored (Friedman 2009; Okeke 2009). Conventional surgical techniques such as trabeculectomy are associated with significant risks, with more than 40% of patients developing perioperative complications (Kirwan 2013; Lichter 2001) and reoperation being needed in 7% to 18% (Gedde 2012; Kirwan 2013). Therefore, they are often reserved for disease that is progressing despite other treatments (King 2013).

Description of the intervention
Recently, a number of minimally-invasive surgical techniques have been developed, with the aim of achieving long-term reduction of IOP with a better safety profile than conventional surgery (Francis 2011). Among them, ab interno trabecular bypass surgery with Hydrus Schlemm’s canal Microstent (Ivantis Inc., Irvine, California) is a CE marked treatment.

**How the intervention might work**

The trabecular meshwork is the main site of resistance to outflow from the eye of aqueous humour (Overby 2009). The Hydrus Microstent is an 8 mm long crescent-shaped open structure, curved to match the shape of Schlemm’s canal. This is intended to promote outflow of aqueous humour, and thereby reduce IOP. The microstent is implanted ab interno through a clear corneal incision into Schlemm’s canal using a preloaded hand-held injector. After being implanted, the microstent bypasses the trabecular meshwork and dilates Schlemm’s canal over three clock hours to provide direct aqueous access from the anterior chamber to multiple collector channels (Pfeiffer 2015).

**Why it is important to do this review**

Consultation with patients and healthcare professionals has identified a need for better treatments for glaucoma (James Lind Alliance 2013). Minimally-invasive glaucoma procedures carry the possibility of safe and effective long-term reduction of IOP, removing concerns about permanent vision loss due to nonadherence to eye-drops. A single treatment may also be more acceptable to patients than daily and indefinite self-administration of eye-drops. To date, approximately 2,700 treatments have been performed worldwide in either feasibility studies, randomised controlled trials, or data registries (Ivantis Inc., on file). In the light of the potential benefits for patients and the widespread uptake of the technique, it is important to critically evaluate the evidence for the efficacy and safety of treatment with Hydrus. Importantly, Hydrus implantation surgery may be combined with phacoemulsification (cataract surgery), a sight-restoring operation to remove the natural lens of the eye when it has lost clarity. Since phacoemulsification itself reduces IOP (Mansberger 2012), we will specifically examine the evidence for efficacy of Hydrus treatment in people who have concomitant phacoemulsification in comparison to those who do not have concomitant phacoemulsification.

**OBJECTIVES**

The main objective is to assess the results at two years of ab interno trabecular bypass surgery with Hydrus for OAG in comparison to conventional medical, laser, or surgical treatment in terms of efficacy and safety. A secondary objective will be to examine the effects of Hydrus surgery in people who have concomitant phacoemulsification in comparison to those who do not have concomitant phacoemulsification.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include randomised controlled trials (RCTs) only. We will include reports of RCTs prepared in any language irrespective of their publication status.

**Types of participants**

Participants will have OAG of any type, including primary and secondary OAG. Closed angle glaucoma will be excluded. As there are no universally-accepted criteria by which glaucoma may be defined, we will permit studies to use their own definitions of glaucoma (provided these are clearly stated). In addition, participants with ocular hypertension, normal tension glaucoma, or possible glaucoma (suspects for glaucoma) will be included. We will not apply any restrictions regarding location, setting, or demographic factors.

**Types of interventions**

The intervention will be ab interno trabecular bypass surgery with Hydrus (Ivantis Inc., Irvine, California). We will compare ab interno trabecular bypass surgery with Hydrus to:

1. laser treatment (selective laser trabeculoplasty or argon laser trabeculoplasty);
2. other MIGS techniques;
3. conventional glaucoma surgery (trabeculectomy);
4. medical therapy; or
5. in combination with phacoemulsification compared with phacoemulsification alone (since phacoemulsification cataract surgery is known to reduce IOP (Mansberger 2012)).
Types of outcome measures
We will not use the reporting of particular outcomes as a criterion for eligibility for review. We will not exclude studies from review solely on the grounds of an outcome of interest not being reported.

Primary outcomes
The primary outcome will be the proportion of participants who are drop-free (not using eye-drops) at two years after randomisation.

Several different glaucoma outcome measures have been specified as primary outcomes in other Cochrane Reviews and protocols (Ismail 2015). A recent study classified IOP, visual field, safety, and anatomic outcomes as being highly important to glaucoma experts (Ismail 2016). A panel of patients from the Patient and Public Involvement Group of the National Institute for Health Research (NIHR) Biomedical Research Centre for Ophthalmology identified drop-free disease control as a highly valued outcome (unpublished). We chose a participant-centred primary outcome.

Secondary outcomes
Secondary outcomes will be:
1. Mean change in IOP, measured using Goldmann applanation tonometry, from randomisation to two years.
2. The proportions of participants experiencing intra- and postoperative complications from randomisation to two-year follow-up, including but not restricted to the following:
   - Loss of visual acuity (more than two Snellen lines or more than 0.3 logMAR, according to the method of recording visual acuity; or loss of light perception).
   - Bleeding, as recorded by the investigators.
   - Endophthalmitis, as recorded by the investigators.
   - IOP spikes (postoperative rise in IOP, measured using Goldmann applanation tonometry, of more than 10 mmHg compared to the previous assessment, including during the first postoperative month).
   - Secondary surgery, as recorded by the investigators.
3. Change in health-related quality of life measure, from randomisation to two-year follow-up.

Search methods for identification of studies

Electronic searches
The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no language or publication year restrictions.
- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue) (Appendix 1);
- MEDLINE Ovid (1946 to present) (Appendix 2);
- Embase Ovid (1980 to present) (Appendix 3);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch (Appendix 4);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 5);

Searching other resources
We will search the reference lists of included studies for other possible studies and will contact any individuals or organisations who, we believe, may have conducted or be conducting relevant RCTs. We will also search the website of the manufacturer (Ivantis Inc., Irvine, California; www.ivantisinc.com) for any information on forthcoming trials.

Data collection and analysis

Selection of studies
Two review authors working independently will screen titles and abstracts of all articles identified by the search using web-based online review management software (Covidence 2015). If abstracts are not available, we will screen full-text articles. Two review authors will independently assess full-text reports of all potentially eligible studies. If there is disagreement regarding eligibility, a third review author will arbitrate. If any full-text reports are rejected, we will record the reasons for this.

Data extraction and management
We will extract data from reports of included studies using a data collection form, which will be developed and piloted on the first five studies included. Two review authors will work independently to extract study characteristics from reports of each study and enter the data into Review Manager 5 (RevMan 5) (Review Manager 5 2014). If there is disagreement, a third independent review author will arbitrate.

We will collect the following information on the characteristics of included studies (Appendix 7):
- Year of publication.
- Year of study.
- Country of study.
- Sample size.
- Participation rate.
- Method of recruitment.
• Eligibility criteria.
• Diagnostic criteria.
• Method of randomisation.
• Method of masking.
• Number of study arms.
• Types of participants.
• Types of interventions.
• Types of comparators.
• Use of phacoemulsification at the same time as the intervention.

We will collect the following data regarding outcomes (Appendix 7):
• IOP at baseline.
• IOP at follow-up.
• Number of glaucoma medications at baseline.
• Number of glaucoma medications at follow-up.
• Intraoperative complications.
• Postoperative complications or secondary surgery.
• Duration of follow-up.
• Loss to follow-up.
• Intervals at which outcomes were assessed.

Where data on included studies are missing or unclear, we will contact the individuals or organisations involved to obtain clarification. We will collect and use the most detailed numerical data available to facilitate analyses of included studies. We will attempt to obtain these data from individuals or organisations in preference to less precise methods such as extracting numeric data from graphs. If this is necessary, two independent review authors will extract the data and a third review author will arbitrate, in case of disagreement.

Assessment of risk of bias in included studies
We will use the latest version of the Cochrane 'Risk of bias' tool as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) to assess the risk of bias and assign judgements of this for included studies.

Measures of treatment effect
The primary outcome is the proportion of participants who are drop-free two years after randomisation. We will use a risk ratio as the treatment effect measure. In assessing this effect measure, we will report how prescribing of IOP-lowering eye-drops was determined during follow-up. We will examine whether the people measuring IOP and those deciding upon the prescribing of IOP-lowering eye-drops were masked to treatment group.

We will report mean change in IOP from randomisation to two years after randomisation. Secondary safety outcomes will be reported as risk ratios. Health-related quality of life outcomes will be reported as differences in means or risk ratios for continuous and binary data, respectively.

Unit of analysis issues
We will assess whether included studies have included one or two eyes from each subject and whether or not randomisation has been conducted at the level of the participant or the eye. There is a potential for medical treatments, such as topical beta blockers used for one eye, to influence the outcome in the other eye (Piltz 2000). Surgery to lower IOP in one eye may also affect the IOP of the fellow eye (Radcliffe 2010). Therefore, we will exclude studies that have adopted a paired design.

Dealing with missing data
We will endeavour to minimize missing outcome data by contacting individuals and organisations to obtain them. If the data are unavailable but the level of missing data in each group and reasons for missing data in each group are similar we may simply analyse available-case data if an intention-to-treat (ITT) analysis has not been performed. We will report if authors have conducted their own ITT analysis despite missing data, but we will document whether they provide any justification for the method they have used to deal with missing data and whether they have compared their ITT result with an available-case result.

Assessment of heterogeneity
We will assess the heterogeneity between trials by careful examination of the study reports, assessing forest plots and an examination of the I² value. We will consider I² values greater than 50% as indicative of substantial heterogeneity, suggestive that meta-analysis might not be wise - however, consideration will be given to the consistency of the effect estimates. If all estimates are in the same direction, we might meta-analyse even where heterogeneity is evident; we will comment on the heterogeneity.

Assessment of reporting biases
We will use a funnel plot to assess the risk of publication bias if there are more than 10 trials within our review.

Data synthesis
We will undertake a meta-analysis where data appear clinically, methodologically, and statistically homogeneous. We will check that participants, interventions, comparators, and outcomes are sufficiently similar to give a clinically meaningful result and that our I² result does not indicate considerable inconsistency (i.e. I² less than 50%). If all estimates are in the same direction, we might meta-analyse even where heterogeneity is evident but will comment on this. We will use a random-effects model unless there are fewer than three eligible studies, in which case, we will use a fixed-effect model.
**Subgroup analysis and investigation of heterogeneity**

We will undertake a subgroup analysis. The effect modifier to be examined will be use of phacoemulsification as a cointervention. Phacoemulsification has been shown to reduce IOP (Mansberger 2012). We will therefore analyse whether the effect of Hydrus surgery differs depending on whether phacoemulsification is used as a cointervention.

**Sensitivity analysis**

We will assess the impact of including studies at high risk of bias for an outcome in one or more key domains.

**Summary of findings**

We will prepare tables to summarise the findings of the review, including the assessment of the certainty of evidence for all outcomes using the GRADE approach (GRADEpro 2014). We will report the following outcomes in the 'Summary of findings' table and the comparison groups described under Types of interventions: ab interno trabecular bypass surgery with Hydrus (Ivantis Inc., Irvine, California) compared with laser treatment, other MIGS techniques, conventional glaucoma surgery (trabeculectomy), medical therapy or in combination with phacoemulsification compared with phacoemulsification alone.

1. Proportion of participants who are drop-free (not using eye-drops) at two years follow-up.
2. Mean change in number of IOP-lowering drops taken per day from baseline to two years follow-up.
3. Mean change in IOP, measured using Goldmann applanation tonometry, from baseline to two years follow-up.
4. Health-related quality of life at two years follow-up.
5. Intraoperative complications.
6. Postoperative complications, up to two years follow-up.
7. Secondary glaucoma surgery, including laser, as recorded by the investigators of the included trials between baseline and two years follow-up.

**ACKNOWLEDGEMENTS**

Cochrane Eyes and Vision (CEV) will create and execute the electronic search strategies. We thank Nitin Anand and Jennifer Evans for their comments on the published protocol that forms the template for this one (Hu 2016) and Anupa Shah for assisting with the review process.

We thank the members of the MIGS Consortium for their input in this protocol.

**REFERENCES**

**Additional references**

AGIS 2000


Burr 2007


CNTG Study Group 1998


Covidence 2015 [Computer program]


Francis 2011


Friedman 2009


Gedde 2012


Glanville 2006


GRADEpro 2014 [Computer program]

Ab interno trabecular bypass surgery with Schlemm’s Canal Microstent (Hydrus) for open angle glaucoma (Protocol)

Heijl 2002

Higgins 2011

Hu 2016

Ismail 2015

Ismail 2016

James Lind Alliance 2013

Kass 2002

King 2013

Kirwan 2013

Lichter 2001

Mansberger 2012

Okeke 2009

Overby 2009

Peters 2013

Pfeiffer 2015

Piltz 2000

Quigley 2006

Radicke 2010

Review Manager 5 2014 [Computer program]

* Indicates the major publication for the study
A P P E N D I C E S

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
#2 MeSH descriptor: [Intraocular Pressure] explode all trees
#3 MeSH descriptor: [Ocular Hypertension] explode all trees
#4 OAG or POAG or IOP or OHT
#5 simple near/3 glaucoma*
#6 open near/2 angle near/2 glaucoma*
#7 chronic near/2 glaucoma*
#8 secondary near/2 glaucoma*
#9 low near/2 tension near/2 glaucoma*
#10 low near/2 pressure near/2 glaucoma*
#11 normal near/2 tension near/2 glaucoma*
#12 normal near/2 pressure near/2 glaucoma*
#13 pigment near/2 glaucoma*
#14 MeSH descriptor: [Exfoliation Syndrome] this term only
#15 exfoliat* near/2 syndrome*
#16 exfoliat* near/2 glaucoma*
#17 pseudoexfoliat* near/2 syndrome*
#18 pseudoexfoliat* near/2 glaucoma*
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 Schlemm* near/4 (microstent* or scaffold*)
#21 Hydrus
#22 #20 or #21
#23 #19 and #22

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly,ab,ti.
6. trial,ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle/
14. exp intraocular pressure/
15. ocular hypertension/
16. (OAG or POAG or IOP or OHT).tw.
17. (simple$ adj3 glaucoma$).tw.
18. (open adj2 angle adj2 glaucoma$).tw.
19. (primary adj2 glaucoma$).tw.
20. (chronic adj2 glaucoma$).tw.
22. (low adj2 tension adj2 glaucoma$).tw.
23. (low adj2 pressure adj2 glaucoma$).tw.
24. (normal adj2 tension adj2 glaucoma$).tw.
25. (normal adj2 pressure adj2 glaucoma$).tw.
27. exfoliation syndrome/
29. (exfoliat$ adj2 glaucoma$).tw.
30. (pseudoexfoliat$ adj2 syndrome$).tw.
31. (pseudoexfoliat$ adj2 glaucoma$).tw.
32. or/13-31
33. (Schlemm$ adj4 (microstent$ or scaffold$)).tw.
34. Hydrus.tw.
35. or/33-34
36. 32 and 35
37. 12 and 36
The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. open angle glaucoma/
Appendix 4. ISRCTN search strategy
(Schlemm's canal microstent OR Schlemm's canal scaffold OR HYDRUS)

Appendix 5. ClinicalTrials.gov search strategy
(Schlemm's canal microstent OR Schlemm's canal scaffold OR HYDRUS)

Appendix 6. WHO ICTRP search strategy
Schlemm's canal microstent OR Schlemm's canal scaffold OR HYDRUS

Appendix 7. Data on study characteristics

<table>
<thead>
<tr>
<th>Mandatory items</th>
<th>Optional items</th>
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<tr>
<td><strong>Methods</strong></td>
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<tr>
<td>Study design</td>
<td><em>Parallel group RCT</em> <em>i.e. people randomised to treatment</em></td>
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<td></td>
<td><em>Within-person RCT</em> <em>i.e. eyes randomised to treatment</em></td>
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<td></td>
<td><em>Cluster RCT</em> <em>i.e. communities randomised</em></td>
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<td>Number of study arms</td>
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<td>Method of randomisation</td>
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<td>Exclusions after randomisation</td>
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<td>Losses to follow-up</td>
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<td>Number randomised/analysed</td>
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### Participants

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<tr>
<th>Total number of participants</th>
<th>Number (%) of men and women</th>
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<td>Number (%) of men and women</td>
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<th>Average age and age range</th>
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### Interventions

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<th>Comparator parameters, e.g. dosage of drugs</th>
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<th>Number of people randomised to this group</th>
<th>Intervention name</th>
<th>Comparator name</th>
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<tr>
<th>Number of glaucoma medications at baseline</th>
<th>Planned/actual length of follow-up</th>
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### Outcomes

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**Notes**

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**Contributions of Authors**

Francisco Otarola, Kuang Hu and Catey Bunce wrote the protocol. All authors reviewed and approved the protocol.

**Declaration of Interest**

The authors are seeking funding to address the subject of this review.

Kuang Hu performs minimally-invasive glaucoma surgery. He has lectured on ‘Constructing clinical trials for MIGS - the lack of evidence and what to do about it’ at the Moorfields International Glaucoma Symposium 2016, sponsored by Laboratoires Thea, which is contributing an educational grant to Moorfields Eye Hospital.

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External sources

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