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Ab interno trabecular bypass surgery with iStent for open angle glaucoma

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Abstract

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

The primary objective is to assess the comparative effectiveness and safety of ab interno trabecular bypass surgery with iStent or iStent inject for OAG in comparison to conventional medical, laser, or surgical treatment. A secondary objective is to examine the effectiveness and safety of iStent or iStent Inject surgery in people who have concomitant phacoemulsification.

BACKGROUND

Description of the condition

Glaucoma describes a group of diseases characterized by clinical and histopathological manifestations of optic nerve damage leading to irreversible vision loss (Allingham 2010). Glaucoma is the second leading cause of blindness, affecting approximately 60 million people worldwide (Quigley 2006). A recent systematic review estimated that the global prevalence of glaucoma in people between 40 and 80 years of age may increase to 76 million by 2020 and to 111.8 million by 2040 (Tham 2014). Open angle glaucoma (OAG) is the most common type of glaucoma and accounts for approximately 74% of all glaucoma cases (Quigley 2006). Women comprise 55% of OAG cases, and OAG disproportionately affects people of African ancestry and older adults (NEI 2015).

While most patients with OAG exhibit elevated intraocular pressure (IOP) upon repeated measurement, IOP is not a direct measure of structural or functional glaucomatous optic neuropathy and not all patients with glaucoma present with elevated IOP (AAO 2015; Le 2016; Medeiros 2015). Nevertheless, because IOP is the only known modifiable risk factor,

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CONTRIBUTIONS OF AUTHORS

Jimmy Le wrote the protocol. All authors reviewed and approved the protocol.

DECLARATIONS OF INTEREST

No financial interests to declare.

treatment for OAG has focused predominantly on lowering IOP to slow disease progression and decrease the rate of visual field loss (Li 2016; Quigley 2007).

Description of the intervention

Lowering IOP is achieved through medical, laser, and surgical interventions, typically implemented in a step-wise fashion (AAO 2015; NICE 2009). Since the early 2000s, a series of new treatment modalities, which the US Food and Drug Administration (FDA) refers to as "minimally invasive glaucoma surgical" (MIGS) devices, has emerged. MIGS are ab interno procedures requiring minimal to no conjunctival manipulation or scleral dissection, which can be safely performed at the time of another intraocular procedure, specifically cataract extraction by phacoemulsification. They improve aqueous outflow, as traditional filtering surgeries do, but typically to a more modest degree than trabeculectomy or tube shunt implantation and with fewer risks than those more invasive surgeries (Caprioli 2015; Francis 2011; Spaeth 2015). While MIGS interventions are not generally used as first-line therapy at this time, they may reduce the need for medication.

Examples of MIGS interventions include the iStent and iStent Inject, Trabectome ab interno trabeculectomy, endoscopic cyclophotocoagulation (ECP), gonioscopy-assisted transluminal trabeculotomy (GATT), the Hydrus Microstent intracanalicular scaffold, the XEN Gel Stent and the Innfocus Microshunt. Of these, the first four are currently FDA approved for use in the United States; the others are being evaluated in clinical trials.

This Cochrane review will examine the iStent and iStent inject (Glaukos Corporation, Laguna Hills, CA, USA), the former of which was the first MIGS device to have received FDA approval, for people with mild to moderate OAG.

- The iStent is a heparin-coated non-ferromagnetic titanium "L-shaped" device, 1 mm in length with a head facing the anterior chamber 0.3 mm in height (Glaukos 2016). This MIGS device is preloaded into a single-use injector and then inserted ab interno through the trabecular meshwork under direct gonioscopic view (Manasses 2016). The iStent creates a permanent opening that directly connects the anterior chamber to Schlemm's canal.
- The iStent inject is a much smaller, second-generation "mushroom-shaped" MIGS device, 360 μm in length with a conical head with maximum width of 230 μm. Like the iStent, the iStent inject is made of heparin-coated titanium but the conical head contains four evenly spaced outlets that allow fluid to pass through the anterior chamber into Schlemm's canal (Bahler 2012). The injector is preloaded with two iStent inject MIGS devices and is designed to deliver both stents, ab interno, into Schlemm's canal while entering the eye only once (Bahler 2012; Klamann 2015).

How the intervention might work

IOP increases when there is an imbalance between production and outflow of aqueous humor, a clear fluid that provides avascular ocular structures with nutrition. Aqueous humor

drains through a complex network of cells and tissue (trabecular meshwork, Schlemm's canal, and collector channels) in an area known as the drainage angle (AAO 2015).

Given that the trabecular meshwork is the primary site of aqueous outflow and that resistance to aqueous humor outflow in this region largely determines IOP (Manasses 2016), bypassing the trabecular meshwork is a viable method to decrease IOP. Ab interno implantation of MIGS devices such as the iStent and iStent inject may increase outflow facility by providing direct access via a permanent opening through the walls of Schlemm's canal and to the collector channels (Francis 2011).

Why it is important to do this review

Reducing IOP may prevent vision loss in people with mild to moderate OAG, and most treatment of OAG relies primarily on lowering IOP through medical treatment, laser, or surgery (AAO 2015; AGIS 2000; EGS 2014). Although most people with mild to moderate OAG elect to start with medical treatment (e.g. topical eye drops) as first line of therapy (AAO 2015; NICE 2009), commercially available eye drops have short durations of effect and notoriously poor adherence (Friedman 2009; Okeke 2009). Conventional surgical procedures to alter the trabecular meshwork and drainage angle (such as trabeculectomy) and tube shunts or valves are associated with variable frequencies of success and complications (Gedde 2012a; Gedde 2012b; Spaeth 2015). Several studies have suggested that trabeculectomies fail after about five years in approximately 50%of cases (Gedde 2012a;Gedde 2012b; Kirwan 2013; Lichter 2001). Laser trabeculoplasty (LTP) represents an intermediate intervention between drops and surgery, but its efficacy has been noted to decrease over time and most people ultimately require repeat LTP or surgery (Leahy 2015; Patel 2015; Woo 2015).

At the same time, there is longer termaspiration that a simple, safe, easy to use device can be found as a long term solution to glaucoma control. MIGS procedures are becoming increasingly common, with their proponents claiming better safety profiles than other glaucoma devices and surgical techniques (Brandao 2013; Larsen 2016). In this review, we plan specifically to examine the evidence for efficacy of one type of MIGS devices - the iStent and iStent inject - in people with mild to moderate OAG of any type. This Cochrane review will be conducted in parallel with other reviews currently undertaken by the Cochrane Eyes and Vision MIGS Consortium, which includes MIGS techniques and devices such as the Trabectome (NeoMedix, Tustin, California), Hydrus Microstent (Invantis, Irvine, California) (Otarola 2017), endoscopic cytophotocoagulation (ECP) (Endo Optiks, Waltham, Massachusetts) (Tóth 2017), and XEN Glaucoma Implant (Aque-Sys Implant, Aliso Viejo, California) (King 2017).

OBJECTIVES

The primary objective is to assess the comparative effectiveness and safety of ab interno trabecular bypass surgery with iStent or iStent inject for OAG in comparison to conventional medical, laser, or surgical treatment. A secondary objective is to examine the effectiveness and safety of iStent or iStent Inject surgery in people who have concomitant phacoemulsification.

METHODS

Criteria for considering studies for this review

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

Types of participants—We will include studies of participants with mild to moderate OAG of any type, including primary and secondary OAG. In the absence of a universally-accepted definition for glaucoma, we will permit studies to use their own criteria to define OAG; however, studies of participants with angle-closure glaucoma (where increased pressure in the anterior chamber of the eye occurs because of a blockage of normal circulation of fluid at the junction of the cornea with the iris) will be excluded. In addition, we will allow studies that only included participants with ocular hypertension, normal tension glaucoma, or possible OAG (i.e. suspects).

Types of interventions—We will include studies that compared iStent or iStent inject (Glaukos Corporation, Laguna Hills, CA, USA) to:

1. laser treatment (selective laser trabeculoplasty or argon laser trabeculoplasty)
2. other MIGS procedures/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; Zhang 2015)).

Additionally, we will conduct stratified analyses based on iStent procedures (e.g. iStent versus iStent inject).

Types of outcome measures—We will not use reporting of particular outcomes as a criterion for including a trial into our systematic review. We have adapted our primary and secondary outcomes from a Cochrane review prepared by Hu 2016.

Primary outcomes

- Proportion of participants who are drop-free (not using eye drops) at two years follow-up.

Secondary outcomes

- Mean change in number of IOP-lowering drops taken per day from baseline to two years follow-up.
- Mean change in IOP, measured using Goldmann applanation tonometry, from baseline to two years follow-up.

- Any health-related quality of life measures at two years follow-up, measured as mean change from baseline or proportion meeting a threshold, as defined by the investigators of the included trials.

Adverse outcomes

1. Proportions of participants experiencing intra- and postoperative complications from baseline to two-year follow-up, including but not restricted to the following:
    - **i.** Loss of visual acuity of more than two Snellen lines or more than 0.3 logMAR, according to the method of recording visual acuity; or loss of light perception.
    - **ii.** Bleeding, as recorded by the investigators.
    - **iii.** Endophthalmitis, as recorded by the investigators.
    - **iv.** IOP spikes, defined as 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.
    - **v.** Secondary glaucoma surgery, including laser, as recorded by the investigators of the included trials.

Search methods for identification of studies

Electronic searches—The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomized 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);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 6);
- U.S. Food and Drugs Administration (FDA) website (www.fda.gov) (Appendix 7).

Searching other resources—We will search the reference lists of included studies for possible studies and will contact individuals or organizations, such as the American Glaucoma Society whom we believe may have conducted or be conducting relevant RCTs.

We will also search the website of the manufacturer (Glaukos 2016) for information regarding forthcoming trials.

Data collection and analysis

Selection of studies—After duplicates are removed from the search results, two review authors working independently will screen titles and abstracts of all records identified by the search using web-based review management software (Covidence 2015). The review authors will classify each record as either relevant or not relevant for full-text review. Two review authors will independently assess the full-text copies of all studies that they identified as relevant during title and abstract screening to determine if the studies meet the inclusion criteria. We will contact the trial authors to clarify any details necessary to make a complete assessment of the eligibility, and we will document reasons for exclusion for each study assessed as not eligible after review of the full-text articles. We will resolve all discrepancies between review authors by discussion at each stage of the screening process.

Data extraction and management—Two review authors working independently will extract data using a web-based electronic data collection form. We will extract the information as described in Appendix 8, including: study setting, countries where recruitment took place, sample size, study duration and follow-up time, study design, analysis choice, sources of funding, and potential conflicts of interests, characteristics of the participants (e.g., inclusion/exclusion criteria), underlying disease conditions, and medical history (including IOP at baseline, number of glaucoma medications at baseline, visual acuity and other vision-related characteristics), interventions (e.g. iStent or iStent inject) and comparators (e.g. type of laser, drugs, surgery, duration, and timing), outcomes (e.g. domain, specific measurement, specific metric, method of aggregation, and the time frame), and quantitative results.

The two authors will compare the extracted data and resolve any discrepancies by discussion. One review author will complete data entry into Review Manager 5 (RevMan 5) (Review Manager 5 2014) and a second author will verify the data entered.

Assessment of risk of bias in included studies—Two review authors working independently will assess the risk of bias in included studies, following guidance described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Specific items for consideration will include random sequence generation and allocation concealment (selection bias), masking of participants and study personnel (performance bias), masking of outcome assessors (detection bias), missing data and intention-to-treat analysis (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. We will assign each item as having 'low risk', 'high risk', or, if the information provided is insufficient to make an assessment, 'unclear risk'. We will document reasons for those assessments and resolve any discrepancies through discussion. We will present the overall assessments as the 'Risk of bias' summary figure and graph (Higgins 2011).

Measures of treatment effect—We will use a mean difference as the measure of effect for all continuous outcomes, including the change in number of eye drops, IOP, and possibly quality of life. We will use risk ratio as the measure of effect for all binary and categorical outcomes, including the proportion of participants who are drop-free, safety outcomes, and possibly quality of life.

Unit of analysis issues—We will assess whether the included studies have included one or both eyes from each participant and whether or not study investigators randomized at the participant-level or at the eye-level. Since certain medical treatments, such as topical beta blockers when used in one eye, have the potential to influence the outcome in the contralateral eye, we will exclude studies adopting a paired design.

Dealing with missing data—Where data on included studies are unclear or missing, we will write to the authors. Should there be no response within 2 weeks, we will analyze the data using the best information available. When individual participant data are available, we will consider multiple imputation or other imputation approaches for handling missing data. In the event that the quality of the available data prevents any meaningful analysis, we will omit the study from quantitative analyses and note this decision in the discussion.

Assessment of heterogeneity—We will assess clinical and methodological heterogeneity by examining participant characteristics, MIGS techniques and devices, and outcomes by carefully reviewing the study report and taking into consideration potential risk of bias. We will assess forest plots and examine the I^2 value and its confidence interval. Similar to other protocols on MIGS procedures, we will consider an I^2 value greater than 50% as indicative of substantial heterogeneity, suggesting that a meta-analysis may not be appropriate; however, we will give consideration to the consistency of the effect estimates. For example, if all estimates are in the same direction, we may report a meta-analysis even in the presence of substantial statistical heterogeneity and will comment on the heterogeneity.

Assessment of reporting biases—We will assess publication bias using funnel plots if there are more than 10 trials that met the eligibility criteria for this review. We will assess selective reporting as part of the 'Risk of bias' assessment.

Data synthesis—We will follow Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* for data synthesis and analysis (Deeks 2011). We will use random-effects models to compute quantitative syntheses. We will provide a descriptive, qualitative synthesis of studies and their results. We will examine comparisons between iStent or iStent inject without phacoemulsification versus conventional glaucoma treatment (e.g. medical therapy, laser treatment, or conventional glaucoma surgery) or phacoemulsification alone; between iStent or iStent inject with phacoemulsification versus conventional glaucoma treatment or phacoemulsification alone; and between iStent versus iStent inject, separately.

Subgroup analysis and investigation of heterogeneity—We will undertake a subgroup analysis according to whether or not phacoemulsification was a co-intervention.

We will conduct analysis by subgroups for type of treatment in the interventiongroup (iStent or iStent inject).

Sensitivity analysis—We will conduct additional sensitivity analyses to determine the impact of any post hoc decisions made during the review process.

Summary of findings—We will prepare tables to summarize the findings of this review. We will use the GRADE approach to assess the certainty of the evidence (GRADEpro 2014). We will include the following outcomes in the summary and the comparison groups described under Types of Intervention: iStent or iStent inject compared with laser treatment, other MIGS procedures/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.

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APPENDICES

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*

#14MeSH 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 MeSH descriptor: [Stents] explode all trees

#21 iStent

#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.

21. (secondary 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.

26. (pigment$ adj2 glaucoma$).tw.

27. exfoliation syndrome/

28. (exfoliat$ adj2 syndrome$).tw.

29. (exfoliat$ adj2 glaucoma$).tw.

30. (pseudoexfoliat$ adj2 syndrome$).tw.

31. (pseudoexfoliat$ adj2 glaucoma$).tw.

32. or/13–31

33. exp Stents/

34. istent.tw.

35. 33 or 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 randomizations/

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/

13. (clin$ adj3 trial$).tw.

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/

34. intraocular pressure/

35. intraocular hypertension/

36. (OAG or POAG or IOP or OHT).tw.

37. (open adj2 angle adj2 glaucoma$).tw.

38. (primary adj2 glaucoma$).tw.

39. (chronic adj2 glaucoma$).tw.

40. (secondary adj2 glaucoma$).tw.

41. (low adj2 tension adj2 glaucoma$).tw.

42. (low adj2 pressure adj2 glaucoma$).tw.

43. (normal adj2 tension adj2 glaucoma$).tw.

44. (normal adj2 pressure adj2 glaucoma$).tw.

45. (pigment$ adj2 glaucoma$).tw.

46. exfoliation syndrome/

47. (exfoliat$ adj2 syndrome$).tw.

48. (exfoliat$ adj2 glaucoma$).tw.

49. (pseudoexfoliat$ adj2 syndrome$).tw.

50. (pseudoexfoliat$ adj2 glaucoma$).tw.

51. or/33–50

52. Stent/

53. istent.tw.

54. 52 or 53

55. 51 and 54

56. 32 and 55

Appendix 4. ISRCTN search strategy

iStent

Appendix 5. ClinicalTrials.gov search strategy

iStent

Appendix 6. WHO ICTRP search strategy

iStent

Appendix 7. FDA search strategy

istent AND random OR randomly OR randomised OR randomized

Appendix 8. Data on study characteristics

Mandatory items		**Optional items**
Methods		
Study design	• **Parallel group RCT** *i.e. people randomized to treatment* • **Within-person RCT** *i.e. eyes randomized to treatment* • **Cluster RCT** *i.e. communities randomized to treatment* • **Cross-over RCT** • Other, specify	Number of study arms Method of randomization Exclusions after randomization Losses to follow up Number randomized/ analyzed Method of masking How were missing data handled? *e.g. available case analysis, imputation methods* Reported power calculation (Y/N), *if yes, sample size and power* Unusual study design/ issues
Eyes Unit of randomization/ unit of analysis	• **One eye included in study**, *specify how eye selected* • **Two eyes included in study, both eyes received same treatment**, *briefly specify how analyzed (best/worst/ average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture of one eye and two eyes* • **Two eyes included in study, eyes received different treatments,** *specify if correct pair-matched analysis done*	
Participants		
Country		Setting Ethnic group Method of recruitment
Total number of participants	*This information should be collected for total study population recruited into the study. If these data are reported for the people who were followed up only, please indicate.*	
Number (%) of men and women		Number (%) of men and women

Mandatory items		**Optional items**
Average age and age range Inclusion criteria		Average age and age range
Exclusion criteria		
Interventions		
Intervention (n=) Comparator (n=) ***See MECIR 65 and 70***	• Number of people randomized to this group • Intervention name • Comparator name • Specify whether phacoemulsification, or other intervention, performed at same time as intervention	iStent or iStent inject surgical parameters, *e. g. degrees of meshwork ablated, electrosurgical power* Comparator parameters, *e.g. dosage of drugs*
Outcomes		
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	• Proportion of participants who are dropfree at 2 years follow-up • Mean change in number of IOP-lowering drops taken per day from baseline to 2 years follow-up • Mean change in IOP from baseline to 2 years follow-up • Health-related quality of life measures at 2 years follow-up • Intraoperative complications Adverse events reported (Y/N)	Planned/actual length of follow-up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)* Date of publication Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest ***See MECIR 69***		