

BMJ Open Comparison of Hydrus and iStent microinvasive glaucoma surgery implants in combination with phacoemulsification for treatment of open-angle glaucoma: systematic review and network meta-analysis

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ABSTRACT

Objectives To compare the efficacy and safety of two Schlemm's canal-based microinvasive glaucoma surgery (MIGS) devices, the Hydrus Microstent and the iStent Trabecular Bypass combined with phacoemulsification for treatment of open-angle glaucoma.

Design Systematic review and network meta-analysis.

Methods Literature searches were conducted on PubMed, Web of Science, Cochrane Library and ClinicalTrials.gov to identify randomised controlled trials (RCTs) assessing the Hydrus or the iStent implantation combined with phacoemulsification for treatment of open-angle glaucoma until September 2020. Risk of bias was assessed using a six-item modified Jadad scale. Effects were estimated using the intraocular pressure (IOP) reduction (IOPR), the percentage of IOPR and the proportion of medication-free patients at follow-up end. Safety was estimated using the proportions of adverse events. The network meta-analysis was conducted within a Bayesian framework using the Markov Chain Monte Carlo method in ADDIS software.

Results Six prospective RCTs comprising 1397 patients were identified. Regarding the absolute value and the percentage of IOPR, the Hydrus and 2-iStent implantation combined with phacoemulsification were significantly more effective than phacoemulsification alone. Rank probability analysis revealed the Hydrus might be the best choice to lower IOP. There was no significant difference in the proportion of medication-free patients among groups. The Hydrus and 2-iStent implantation had a higher probability to achieve the medication-free status versus the 1-iStent implantation and phacoemulsification alone. Overall safety profiles were good for each device with the focal peripheral anterior synechiae more frequently reported in Hydrus eyes.

Conclusions The Hydrus implantation may have a slight advantage over the 1-iStent or 2-iStent implantation in combination with phacoemulsification to treat open-angle glaucoma. Our findings might be of some uncertainty due to the limited included data. Further studies are needed to investigate whether our findings are robust, including high-quality RCTs to directly compare these MIGS devices.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This meta-analysis included the most recent reports.
- ⇒ We systematically identified and rigorously collected the available evidence to perform a comprehensive comparison of two Schlemm's canal-based microinvasive glaucoma surgery implants.
- ⇒ The number of included studies is relatively small. Further research is needed to replenish this meta-analysis to offer more convincing conclusion.
- ⇒ The details of adverse events were not always reported in each study.

INTRODUCTION

Glaucoma is a leading cause of irreversible vision loss in the world. Although the pathogenesis of glaucoma is not fully clear, the level of intraocular pressure (IOP) has been closely associated with the retinal ganglion cell degeneration in glaucoma.¹ Reduction of IOP (IOPR) is the only proven and generally accepted method to treat glaucoma in slowing disease progression.¹⁻⁴ Topical ocular hypotensive medications are usually a first-line choice, however, patient adherence and ocular surface toxicity are major issues with the long-term medical management.⁵ When topical medications or other interventions (such as laser) do not achieve adequate IOPR, incisional surgery has to be considered. Current mainstream procedures, trabeculectomy and aqueous shunts, while highly effective at IOPR, may require quite intense postoperative care for the first 3 months after surgery, and may be associated with several sight-threatening complications.^{1 4 6}

In recent years, new devices and procedures have been developed aiming for safer and less invasive IOPR compared with

conventional glaucoma surgeries.⁷ The microinvasive glaucoma surgery (MIGS) devices, placed ab interno via clear corneal incision, shunt aqueous humour into the Schlemm's canal, the suprachoroidal or subconjunctival space. These devices can be implanted in combination with cataract surgery to treat mild-to-moderate open-angle glaucoma (OAG).⁸ Independent randomised controlled trials (RCTs) have demonstrated that MIGS devices are effective in reducing IOP and medication use with good safety profiles.^{9–17}

In the present network meta-analysis, we aimed to indirectly compare the clinical efficacy and safety of two different Schlemm's canal-based MIGS devices, the Hydrus Microstent (Ivantis, Irvine, California, USA) and the iStent Trabecular Bypass device (Glaukos Corporation, San Clemente, California, USA), combined with phacoemulsification for the treatment of OAG. The Hydrus Microstent is an 8 mm long crescent-shaped open structure, curved to match the shape of Schlemm's canal. The first-generation iStent Trabecular Bypass device is a 1.0 mm long L-shaped stent with a snorkel (inlet) on the short side, which resides in the anterior chamber, and an open half-pipe lumen (foot), which resides in Schlemm's canal. The iStent inject, which is the second generation, preloads two 0.4 mm long, 0.3 mm wide plug-shaped implants with a central opening in its injector for easier insertion. The two-implant design of iStent inject may also reduce the impact of single stent blockage.¹⁸ The clinical efficacy outcomes include the IOPR from baseline to follow-up end, and the proportion of medication-free patients at the end of follow-up. The safety outcomes include the proportion of common adverse events after surgery.

METHODS

This systematic review was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,¹⁹ and the PRISMA network meta-analysis extension statement.²⁰

Patient and public involvement

This systematic review was conceptualised and developed due to the unmet need of mild-to-moderate OAG patients to select an effective and safe treatment for IOPR. We used secondary data from peer-reviewed published articles. Even though there was no direct patient or public involvement in this review, the study compared two Schlemm's canal-based MIGS devices comprehensively based on the existing patient data and aim to aid clinicians to properly consult and treat future patients.

Literature search

We searched PubMed, Web of Science, Cochrane Library and ClinicalTrials.gov to identify relevant studies in September 2020. The following terms were searched in each database: 'iStent', 'trabecular micro-bypass stent', 'trabecular bypass', 'Hydrus', 'Hydrus microstent', or

'schlemm canal microstent' AND 'cataract', 'cataract surgery', or 'phacoemulsification' (see online online supplemental appendix 1 for further details on search strategy). We did not apply limits for language or date of publication. When titles fit our search terms, abstracts were reviewed to exclude irrelevant studies (eg, case reports, reviews or experimental studies). We then carefully read all the remaining articles to determine if they contained data that were applicable to this study. Reference lists of included studies and previous meta-analyses were also manually searched for additional relevant articles.

Inclusion and exclusion criteria

We included studies based on the following criteria: (1) The study was an RCT; (2) Hydrus or iStent implantation combined with phacoemulsification was performed; (3) Participants were diagnosed as OAG; (4) Studies had to report baseline and postoperative IOP and antiglaucoma medication use. Studies that met any of the following criteria were excluded: (1) review article or case report, (2) duplicate publication, (3) describing a study already included (eg, subgroup analysis or mid-term report of a large trial or follow-up report after a trial ends), (4) sufficient information not published (eg, full text not accessible or full text did not contain raw data).

Outcome measures

For efficacy analysis, the primary outcomes were the IOPR and the percentage of (IOPR%). When authors reported the mean and SD of the IOPR, we used them directly. For studies that only reported absolute values of the IOP at baseline and end-point, the IOPR and the SD of the IOPR (SD_{IOPR}) were computed as follows^{21 22}:

$$IOPR = IOP_{baseline} - IOP_{end-point}$$

$$SD_{IOPR} = \left(SD_{baseline}^2 + SD_{end-point}^2 - SD_{baseline} \times SD_{end-point} \right)^{1/2}$$

then the IOPR% and the SD of the IOPR% ($SD_{IOPR\%}$) were estimated by

$$IOPR\% = \frac{IOPR}{IOP_{baseline}} \times 100\%$$

$$SD_{IOPR\%} = \frac{SD_{IOPR}}{IOP_{baseline}} \times 100\%$$

The second outcome measure was the proportion of eyes with complete success, which was defined as targeting end-point IOP (≤ 21 mm Hg or study-specific end-points) without antiglaucoma medication. We assessed safety by considering the proportions of eyes with postoperative adverse events, including device malposition, device obstruction, nonobstructive peripheral anterior synechiae (PAS), hyphema, uveitis/iritis, macular oedema, disc haemorrhage, best-corrected visual acuity (BCVA) loss >2 lines and elevated IOP ≥ 10 mm Hg over baseline.

Risk of bias assessment

The methodological quality of included studies was evaluated independently by two authors (RH and DG) based on the six-item modified Jadad scale.^{23–25} It evaluates the

method of randomisation, blinding, withdrawals and drop-outs, inclusion/exclusion criteria, adverse events and the statistical analysis. According to these criteria, the scale scores range from 0 to 8 points. Studies with a score of 4–8 were deemed to be high quality, and studies with a score of 0–3 were deemed to be low quality. Any disagreement between raters was resolved through discussion with a third author (XW).

Data extraction

The studies' demographic details, participant characteristics, interventions, outcomes and limitations were independently extracted by two authors (RH and DG). If disagreements occurred, XW would check the data again.

Statistical analyses

Our analysis classified Hydrus implantation with phacoemulsification, 1-iStent implantation with phacoemulsification, 2-iStent implantation with phacoemulsification and phacoemulsification alone as separate treatment nodes. The network meta-analysis was performed within a Bayesian framework using the Markov Chain Monte Carlo simulation implemented through the Aggregate Data Drug Information System software (V.1.16.6, Drugis, Groningen, NL).²⁶ We used a consistency model, which was based on 50 000 iterations for each 4 chains with a burn-in period of the first 20 000 iterations. Convergence was assessed using the Brooks-Gelman-Rubin method.²⁷ The measures of treatment effects were the weighted mean difference (WMD) for continuous outcomes and relative risk (RR) for dichotomous outcomes with 95% credible intervals (95% CI) based on the Bayesian statistical inference. Consistency analysis could be conducted in the presence of similarity and homogeneity, and on this basis, we could rank the effect of different treatment strategies. The higher ranking means the better the treatment is probably when considering treatment efficacy. It should be noted that even if the difference in the effect size between treatments is small, clinical decisions to choose treatment can still be guided by the probability of treatment rankings.^{28 29} Inconsistency analysis was also conducted and similar results were obtained (online supplemental tables 1–3).

Traditional pairwise meta-analysis was performed using Stata V.12.0 (StataCorp). We calculated and evaluated the OR and its 95% CI of various study outcomes and merged data with inverse variance model. Forest plots were used to illustrate various study outcomes and their merged data (online supplemental figures 1–3). A statistical evaluation of the heterogeneity of included RCTs was carried out using the I^2 parameter.

RESULTS

Literature search results

The PRISMA flow chart of literature selection in this network meta-analysis is illustrated in figure 1. In total,

177 articles were retrieved through our initial search. After removal of duplicates and irrelevant studies (eg, case reports, reviews or experimental studies), 95 articles remained for full-text review. Eighty-two articles were excluded on full-text review as they were not RCTs (43 studies), did not include interventions of interest (11 studies), or did not report outcomes of interest (28 studies). Full-text examinations excluded seven additional articles as they described an RCT already included (subgroup analysis (three studies), mid-term report (one studies) or follow-up report after a trial ends (two studies)), or did not report sufficient data (one study). Finally, six articles (six RCTs)^{9 11–15} were included in this systematic review and network meta-analysis.

Characteristics and outcomes of included studies

Six studies comprising 1397 eyes with OAG and cataract were included in this meta-analysis. Figure 2 presents the network of eligible comparisons for the network meta-analysis. All included studies were prospective RCT investigations. The follow-up duration ranged from 12 months to 24 months and the patients' age distributions did not vary significantly among studies. The median sample size was 139 eyes (range 33–556). The main characteristics of the included studies are presented in table 1. The baseline characteristics of study populations of included RCTs are presented in table 2.

Methodological quality of included studies

Figure 3 presents the results of risk of bias assessment for each included study. The overall quality scores were good ranging from 5 to 8 (the modified-Jadad score >3). Of the six RCTs, appropriate randomisation methods were described by five studies (83.3%); one study (16.7%) was described as double-blind, three studies (50%) were single-blind and the remaining studies were not blinded (n=2, 33.3%). Of the included studies, the majority provided an adequate description of withdrawals and dropouts (n=5, 83.3%), inclusion/exclusion criteria (n=6, 100%), the method used to assess adverse effects (n=6, 100%) and the methods of statistical analysis (n=6, 100%).

Efficacy

Tables 3 and 4 present the WMD and 95% CI of IOPR and IOPR%, respectively, for all possible comparisons by the network meta-analysis using the consistency model. In terms of the IOPR, the 2-iStent group (1.88, 95% CI 0.41 to 3.62 mm Hg) and the Hydrus group (2.21, 95% CI 0.52 to 3.71 mm Hg) showed greater IOPR than the control group at follow-up end. In terms of the IOPR%, the 1-iStent group (7.65%, 95% CI 0.66% to 15.45%), the 2-iStent group (7.31%, 95% CI 1.14% to 14.60%) and the Hydrus group (8.66%, 95% CI 2.02% to 14.81%) all showed greater IOPR than the control group. There was no significant difference in IOPR and IOPR% among the 1-iStent group, the 2-iStent group and the Hydrus group. Figure 4 presents the rank probabilities of these groups

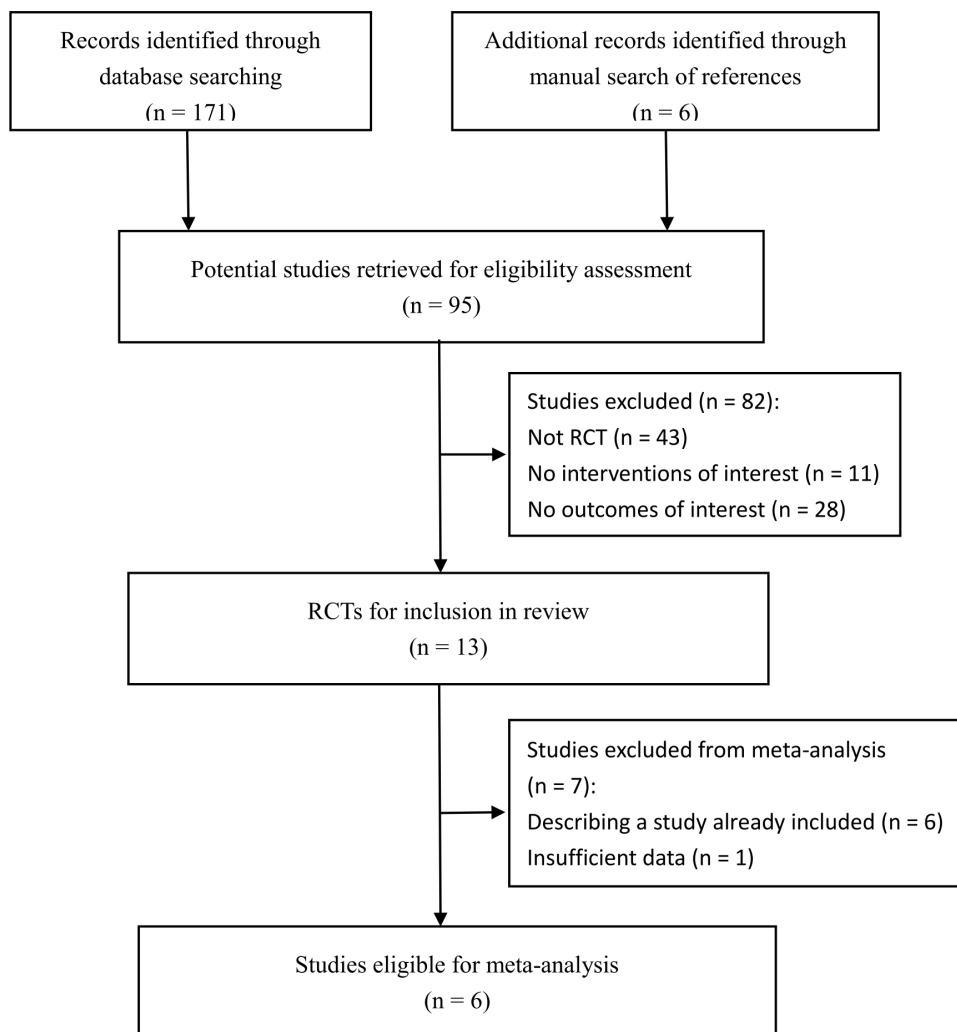


Figure 1 Flow chart of study selection process. RCT, randomised controlled trial.

for the treatment efficacy in terms of the IOPR and the IOPR%. Overall, the Hydrus group showed a higher probability to be the best treatment in lowering IOP than the 1-iStent group and the 2-iStent group (0.60 vs 0.11, 0.60 vs 0.29 in IOPR; 0.46 vs 0.31, 0.46 vs 0.23 in IOPR%, respectively).

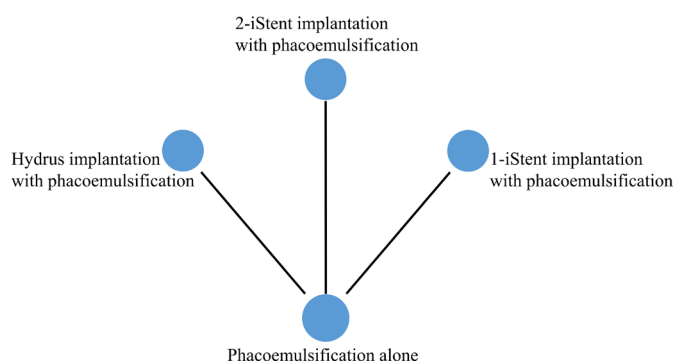


Figure 2 Network graph of all treatment comparisons of included studies. Each node represents a treatment strategy. Lines represent direct comparisons within the randomised controlled trials.

Table 5 presents the RR and 95% CI of the proportions of eyes with complete success for all possible comparisons by the network meta-analysis using the consistency model. The 1-iStent group, the 2-iStent group, and the Hydrus group showed a likely positive effect in the proportions of complete success versus the control group, however, the differences were not statistically significant. There was no significant difference in the proportion of complete success among the 1-iStent group, the 2-iStent group and the Hydrus group. **Figure 4** presents the rank probability of these groups for treatment effect in terms of the proportion of complete success. The 2-iStent group and the Hydrus group showed the higher probability to achieve the complete success than the 1-iStent group and the control group. The 2-iStent group and the Hydrus group showed the close probability to be the best treatment (0.44 and 0.40, respectively).

Adverse events

Main adverse events of included studies are present in **table 6**. In summary, device malposition occurred in 3.9% of 1-iStent eyes, 1.4% of 2-iStent eyes, and was not

Table 1 Study characteristics of included randomised controlled trials

First author (year)	Location	Design	Glaucoma diagnosis	Interventions (no of eyes)	Follow-up (month)
Fea ⁹ (2010)	Italy	Prospective double-masked	POAG	1-iStent (n=12) Control (n=21)	15
Craven ¹¹ (2012)	USA	Prospective open-label	Mild or moderate OAG (POAG 91%)*	1-iStent (n=98) Control (n=101)	24
Fernández-Barrimentos ¹² (2010)	Spain	Prospective open-label	POAG or OHT	2-iStent (n=17)† Control (n=16)	12
Samuelson ¹³ (2019)	USA	Prospective single-masked	Mild to moderate POAG	2-iStent (n=380)‡ Control (n=118)	24
Pfeiffer ¹⁴ (2015)	Multicentre	Prospective single-masked	OAG (POAG 90%) OAG (POAG 82%)	Hydrus (n=44) Control (n=34)	24
Samuelson ¹⁵ (2019)	Multicentre	Prospective single-masked	Mild-to-moderate POAG	Hydrus (n=369) Control (n=187)	24

*The data were presented based on the 1-year follow-up report of the same cohort.¹⁰
 †for Two first-generation stents;
 ‡for Second-generation iStent inject.
 OAG, open-angle glaucoma; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

Table 2 Baseline characteristics of study populations of included randomised controlled trials

First author (year)	Interventions	Age	Female (%)	Ethnicity white (%)	MD (dB)	PSD (dB)	Medicated IOP	Washed-out IOP	No of hypotensive medications
Fea ⁹ (2010)	1-iStent	64.5±3.4	66.7				17.9±2.6		2.0±0.9
	Control	64.9±3.1	–				17.3±3.0		1.9±0.7
Craven ¹¹ (2012)	1-iStent	74±8	59*	71*	-3.8±3.0	2.9±1.8	18.6±3.4	25.4±3.6	1.6±0.8
	Control	73±9			-3.9±3.6	2.8±1.9	17.9±3.0	25.2±3.6	1.5±0.6
Fernández-Barrimentos ¹² (2010)	2-iStent	75.2±7.2	64.7					24.2±1.8	1.1±0.5
	Control	76.7±5.8	43.8					23.6±1.5	1.2±0.7
Samuelson ¹³ (2019)	2-iStent	69.0±8.2	58.1	72.9	-3.4±3.3	3.5±2.5	17.5±3.0	24.8±3.3	1.6±0.8
	Control	70.1±7.7	54.2	72.9	-3.4±3.1	3.3±2.6	17.5±2.8	24.5±3.1	1.5±0.7
Pfeiffer ¹⁴ (2015)	Hydrus	72.8±6.6	60	96	-5.6±5.4	5.1±4.6	18.9±3.3	26.3±4.4	2.0±1.0
	Control	71.5±6.9	42	98	-8.4±7.8	5.2±4.3	18.6±3.8	26.6±4.2	2.0±1.1
Samuelson ¹⁵ (2019)	Hydrus	71.1±7.9	55.8	78.9	-3.6±2.5	3.2±2.2	17.9±3.1	25.5±3.0	1.7±0.9
	Control	71.2±7.6	56.1	81.8	-3.6±2.6	3.1±1.9	18.1±3.1	25.4±2.9	1.7±0.9

Results are mean ±SD unless noted.

 *The data were presented based on the 1-year follow-up report of the same cohort.¹⁰
 IOP, intraocular pressure; MD, mean deviation; PSD, pattern SD.

	Randomized study	Randomization method appropriate	Double blind study	Blinding method appropriate	Description of withdrawals and dropouts	Description of inclusion/exclusion criteria	Method to assess adverse effects described	Methods of statistical analysis described	TOTAL
Fea et al. (2010) ⁹	1	1	1	1	1	1	1	1	8
Craven et al. (2012) ¹¹	1	NR	0	NA	1	1	1	1	5
Fernandez-Barrientos et al. (2010) ¹²	1	1	0	NA	NR	1	1	1	5
Samuelson et al. (2019) ¹³	1	1	0	NA	1	1	1	1	6
Pfeiffer et al. (2015) ¹⁴	1	1	0	NA	1	1	1	1	6
Samuelson et al. (2019) ¹⁵	1	1	0	NA	1	1	1	1	6

Figure 3 Modified-Jadad scores for risk of bias assessment. NA, not applicable; NR, not reported.

reported in Hydrus eyes. Device obstruction occurred in 3.9% of 1-iStent eyes, 6.0% of 2-iStent eyes, and 3.3% of Hydrus eyes. Focal PAS, which was considered as nonobstruction, occurred in 1.7% of 2-iStent eyes, 15.3% of Hydrus eyes and was not reported in 1-iStent eyes.

There were few sight-threatening complications in included studies. At follow-up end, 2.5% of 2-iStent eyes and 1.2% of Hydrus eyes had lost >2 lines compared with preoperative BCVA, however, the proportions were numerically less in treatment eyes than control eyes (3.7% and 1.7%, respectively in 2-iStent and Hydrus studies). Macular oedema occurred in 0.8% of 1-iStent eyes and 2.4% of Hydrus eyes, which were also less in treatment eyes than control eyes (1.4% and 2.5%, respectively in 1-iStent and Hydrus studies). Hyphema, disc haemorrhage, and IOP elevation ≥ 10 mm Hg over baseline occurred at a rate of 2% or less in all treatment eyes of included studies. A higher proportion of postoperative uveitis/iritis was observed in 2-iStent eyes and Hydrus eyes versus control eyes (5.5% vs 3.7% in 2-iStent studies; 5.0% vs 2.9% in Hydrus studies), while a lower proportion of uveitis/iritis was reported in 1-iStent eyes versus control eyes (0.8% vs 4.3%).

DISCUSSION

To our knowledge, this is the first study to indirectly compare the efficacy and safety of two commercially available Schlemm's canal-based MIGS devices for glaucoma management with concurrent cataract surgery using published RCT data. Based on the network meta-analysis, the Hydrus and 2-iStent implantation combined with phacoemulsification achieved statistically greater reductions in IOP than phacoemulsification alone, in terms of either the absolute IOPR values or the percentage. Although no significant difference was found among the three groups, the Hydrus device may provide better IOPR effect than the 1-iStent and 2-iStent device based on the rank probability of the existing data. In terms of the proportion of complete success, no statistically significant difference was found among the 1-iStent group, the 2-iStent group, the Hydrus group and the phacoemulsification alone group, while the rank probability analysis shows the Hydrus and the 2-iStent implantation may achieve the complete success at a higher probability versus the 1-iStent implantation and phacoemulsification alone.

Previous laboratory studies compared the Hydrus and the iStent devices using human cadaveric anterior

Table 3 Network meta-analysis results in IOP reduction at follow-up end

Weighted mean difference (95% CI), mm Hg			
1-iStent			
-0.47 (-2.86 to 1.65)	2-iStent		
-0.81 (-3.02 to 1.64)	-0.35 (-2.34 to 2.25)	Hydrus	
1.40 (-0.19 to 3.06)	1.88 (0.41 to 3.62)*	2.21 (0.52 to 3.71)*	Control

*Statistical significance.
CI, credible interval; IOP, intraocular pressure.

Table 4 Network meta-analysis results in the percentage of IOP reduction at follow-up end

Weighted mean difference (95% CI), %			
1-iStent			
0.32 (-10.02 to 10.27)	2-iStent		
-1.08 (-10.31 to 9.24)	-1.33 (-9.79 to 8.75)	Hydrus	
7.65 (0.66 to 15.45)*	7.31 (1.14 to 14.60)*	8.66 (2.02 to 14.81)*	Control

*Statistical significance.
CI, credible interval; IOP, intraocular pressure.

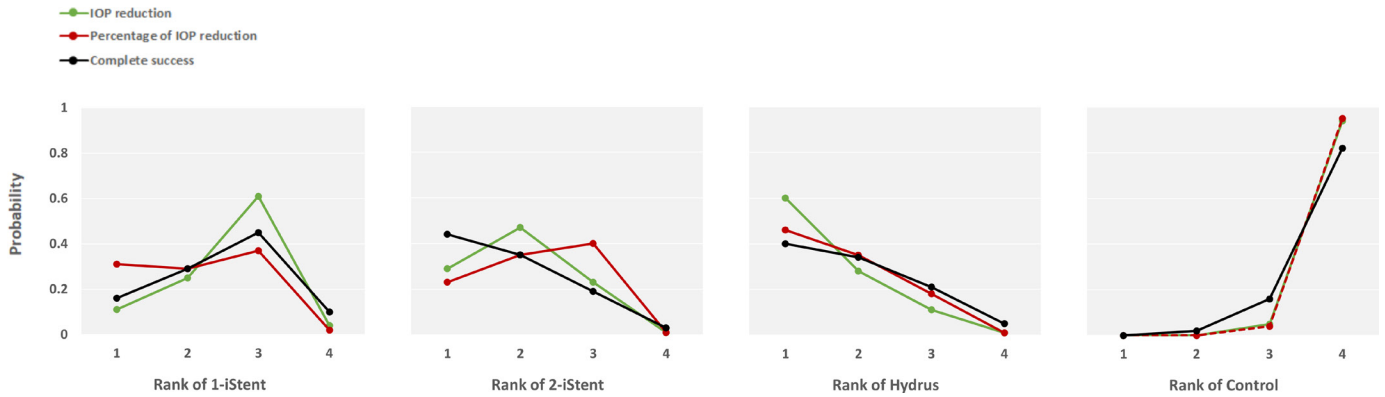


Figure 4 Rank probability of treatments based on the absolute value of intraocular pressure (IOP) reduction, the percentage of IOP reduction, and the proportion of complete success. 1-iStent, 1-iStent implantation with phacoemulsification; 2-iStent, 2-iStent implantation with phacoemulsification; Hydrus, Hydrus implantation with phacoemulsification; Control, phacoemulsification alone. Rank 1 is best and rank 4 is worst.

segment perfusion models.^{30 31} Hays *et al* showed the Hydrus increased the aqueous outflow facility by a greater percentage (73% vs 34%) and at a wider range of perfusion pressures (20–50 mm Hg vs 40 mm Hg) than the two first-generation stents.³⁰ Similar results were shown in a recent randomised paired comparison study by Toris *et al*, in which Hydrus eyes had higher increase in the outflow facility than double iStent inject eyes (79% vs 11%).³¹ These in vitro laboratory findings support our meta-analysis results that the Hydrus device may lower the IOP better than the 2-iStent device. Furthermore, the negative correlation between the Schlemm’s canal area and the IOP has been observed in vivo in OAG eyes, and normal eyes have larger Schlemm’s canal area than OAG eyes.³² Trabecular meshwork stretch is also one of mechanisms of the pilocarpine treatment effect.³³ It is therefore likely that the trabecular meshwork stretch and Schlemm’s canal dilation by the 8 mm scaffold segment of the Hydrus help to provide additional benefits to lower the outflow resistance to collector channels, and accordingly achieve greater reduction in IOP versus the iStent.^{30 31}

Our results are also in line with the conclusion of the COMPARE study, which was a prospective, multicentre RCT to compare the Hydrus and the 2-iStent for stand-alone treatment.³⁴ One hundred and fifty-two eyes from 152 OAG patients were randomised to either Hydrus or two first-generation stents implantation and followed for 12 months. Both groups had significantly reduced

medication use at 12 months compared with the baseline, and the reduction in the Hydrus group was significantly greater by 0.6 medication than the 2-iStent group. More Hydrus patients were medication free at the follow-up end (46.6% vs 24.0%). While it is difficult to directly compare the present meta-analysis results of combined surgery with the stand-alone treatment results, both studies suggest the Hydrus might be more effective to treat OAG versus the 2-iStent.

Two recent retrospective studies compared the real-world outcomes of the Hydrus and the iStent combined with phacoemulsification. For the iStent group, Lee *et al*³⁵ included patients implanted with one first-generation iStent, and Holmes *et al*³⁶ included patients implanted with second-generation iStent inject. Both studies showed sustained IOPR with a good safety profile for the MIGS groups during the 2-year follow-up and no significant difference was found between the Hydrus and the iStent. For medication use, Lee *et al*³⁵ reported a 0.5-medication reduction advantage with the Hydrus group compared with the iStent group, while Holmes *et al*³⁶ reported an additional reduction with the iStent inject group by 0.5 medication on average compared with the Hydrus group. Of note, in the latter study, the Hydrus group had significantly higher IOP, more glaucoma medications, and greater visual field damage at baseline than the iStent inject group, which may potentially bias the results. The baseline visual field mean deviation of Hydrus group in Holmes *et al*’s study was also seemingly greater than that of our included RCTs (−8.8 dB vs −5.6 dB¹⁴/−3.6 dB¹⁵ on average), and their findings are somewhat different to our study. It is unclear whether these differences in efficacy comparison are because of the difference in glaucoma severity of study populations.

The theoretical basis for incremental efficacy with implantation of multiple trabecular stents was established previously based on in vitro perfusion models.^{37–39} Several clinical studies have shown that use of additional first-generation iStent may result in greater IOPR with reduced medication use versus a single implant.^{40–42}

Table 5 Network meta-analysis results in medication free at follow-up end

Relative risk (95% CI) in proportions of complete success			
1-iStent		2-iStent	
0.60 (0.01 to 10.07)			
0.63 (0.04 to 16.37)	1.05 (0.08 to 68.13)	Hydrus	
2.65 (0.37 to 29.48)	4.33 (0.79 to 145.22)	4.06 (0.51 to 38.62)	Control
Complete success, targeting end-point intraocular pressure (≤21 mm Hg or study-specific end-points) without anti-glaucoma medication. CI, credible interval.			

Table 6 Main adverse events after Hydrus and iStent implantation combined with phacoemulsification

Adverse events	1-iStent	1-iStent control	2-iStent	2-iStent control	Hydrus	Hydrus control
No of eyes	128	138	403	135	417	236
Device malposition	3.9%	NA	1.4%	NA	NR	NA
Device obstruction	3.9%	NA	6.0%	NA	3.3%	NA
Focal PAS, nonobstructive	NR	NR	1.7%	NR	15.3%	2.1%
Hyphema	NR	NR	2.0%	NR	0.4%	0.4%
Uveitis/iritis	0.8%	4.3%	5.5%	3.7%	5.0%	2.9%
Macular oedema	0.8%	1.4%	NR	NR	2.4%	2.5%
Disc haemorrhage	0.8%	2.2%	NR	NR	0.2%	NR
BCVA loss >2 lines	NR	NR	2.5%	3.7%	1.2%	1.7%
Elevated IOP ≥10 mm Hg over baseline	NR	NR	2.0%	0.7%	0.9%	3.0%

BCVA, best-corrected visual acuity; IOP, intraocular pressure; NA, not applicable; NR, not reported; PAS, peripheral anterior synechiae.

One study by Hooshmand *et al*¹⁸ did not demonstrate a statistically significant difference between a single iStent and double iStent inject during 1-year follow-up, and earlier recommencement of medications for optimal IOP control was reported with the iStent inject. In this study, the majority of study participants of the 2-iStent group were implanted with the iStent inject. Though there was no significant difference between the 1-iStent group and the 2-iStent group across our outcome measures, the 2-iStent group showed statistically significant reduction in absolute values of IOPR versus phacoemulsification alone, while the 1-iStent group not. Furthermore, the rank probability analysis shows the 2-iStent implantation may achieve complete success at a higher probability than the 1-iStent implantation (0.44 vs 0.16, respectively). Larger population size and longer-term follow-up might be needed to obtain more definitive results for the efficacy comparison between a single first-generation iStent and second-generation iStent inject.

The overall safety profiles of three treatment groups were favourable and few serious ocular adverse events were reported in included RCTs. Device obstruction, which may be caused by pigment, iris tissue or hyphema, occurred in either device (3.9% of 1-iStent eyes, 6.0% of 2-iStent eyes, and 3.3% of Hydrus eyes). Device malposition was observed in 3.9% of 1-iStent eyes and 1.4% of 2-iStent eyes, while not reported in the Hydrus eyes. A likely explanation is the Hydrus was designed with a longer segment residing within the lumen of Schlemm's canal versus the iStent, which allows a better positioning stability. PAS was more frequently observed in the Hydrus eyes versus the 1-iStent and 2-iStent eyes (15.3%, 0%, and 1.7%, respectively). Our result is consistent with the COMPARE study, which indicates that the PAS formation was more common in the Hydrus group.³⁴ It is noteworthy that subgroup analyses of included RCTs did not show the significant difference in the IOPR between eyes with PAS and without PAS.^{14 15} Therefore, most of the PAS might not be obstructive in eyes treated with Hydrus

implantation. Nevertheless, caution should be taken for the PAS as it may eventually result in the device obstruction in the long term.

The baseline characteristics of study populations were overall similar in included RCTs. A common preoperative diagnosis was OAG, including three studies only with primary OAG,^{9 13 15} one study with ocular hypertension (11.8%),¹² one study with pseudoexfoliative glaucoma (6%) and pigmentary glaucoma (3%),¹¹ and one study with pseudoexfoliative glaucoma (10%).¹⁴ Angle-closure, traumatic, uveitic or neovascular glaucoma, or history of incisional glaucoma surgery were all excluded. Baseline visual field damage was comparable in included RCTs, except one Hydrus study with greater mean deviation and pattern SD.¹⁴ Real-world data show that the Hydrus have been used in patients with more advanced disease versus the iStent inject, which are in line with the present included RCT.³⁶ As shown in table 2, the majority of study populations were Caucasian. There was no significant difference in age and sex among groups and these demographics characteristics were well matched for the treatment and control groups in each study.

The surgical techniques of the Hydrus and the iStent are similar which both require a clear view of the angle structure, and the devices are introduced into the anterior chamber through a clear corneal incision and implanted through the trabecular meshwork.³⁴ Despite the increasing use of MIGS in clinical practice, data to compare the cost-effectiveness of these devices remain limited.⁴³ Separate studies have shown either the Hydrus⁴⁴ or the iStent inject^{45 46} combined with phacoemulsification is cost-effective for patients with mild to moderate OAG versus phacoemulsification alone. A recent study by Sood *et al*⁴⁷ compared the cost-effectiveness of the Hydrus and the iStent inject in combination with phacoemulsification for patients with mild to moderate primary OAG. Both devices were not cost-effective versus phacoemulsification alone over the first 2 years due to the initial costs of the surgeries, however, these devices were demonstrated

to be cost-effective treatment options over a lifetime horizon based on the simulation analysis. In comparison, the Hydrus was slightly more cost-effective than the iStent inject, and the authors concluded it was likely due to the slightly better treatment efficacy associated with the Hydrus versus the iStent inject at the identical costs.

Although the results of this meta-analysis may be important for treatment considerations, there are several imitations that should be mentioned. First, we included prospective high-quality RCTs, however, the number of studies is relatively small and the sample size of included studies varied ranging from 33 to 556 eyes, which may potentially bias the results. Further research is necessary to replenish this meta-analysis to offer more convincing conclusion. Second, the details of adverse events were not always reported in each study, and due to the limited data, we did not perform statistical analysis to compare the difference in treatment safety among groups. Third, for the 2-iStent group, we merged the data analysing two first-generation stents¹² and second-generation iStent inject,¹³ which is preloaded with two stents. It is unclear whether there is difference in efficacy between two first-generation stents and double iStent inject, as few studies have been conducted to compare these two stents. In vitro perfusion model study did not demonstrate significant difference in outflow facility increase between the two stents.³¹ A subgroup analysis by Salimi *et al*⁴⁸ shows no significant difference was found between the two generations in terms of IOPR and medication use in eyes with primary angle closure glaucoma.

CONCLUSION

Based on the existing data at present, our network meta-analysis results indicate that the Hydrus device might be slightly more effective in combination with phacoemulsification to treat OAG versus the 1-iStent or 2-iStent device, and these devices have overall good safety profiles. Our findings may aid clinicians in selecting appropriate treatments in glaucoma management, particularly for patients with mild-to-moderate glaucoma and cataract, however, there might be of some uncertainty due to the limited included data. Further prospective, large-scale RCTs that directly compare these MIGS devices combined with cataract surgery are needed to investigate whether our findings are robust.

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