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Network meta-analysis comparison of *Hydrus, Istent* microinvasive glaucoma surgery implants, and phacoemulsification for handling open-angle glaucoma

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Abstract: This study aims to analyze the comparative effectiveness of two Microinvasive Glaucoma Surgery (MIGS) devices, *Hydrus* and *iStent*, in combination with phacoemulsification in patients with open-angle glaucoma. The protocol for this network meta-analysis registered in PROSPERO under registration number CRD42023404273. Literature search was conducted following PRISMA guidelines. RCTs were retrieved from multiple databases based on inclusion and exclusion criteria. Evaluated parameters included intraocular pressure, visual acuity, the number of postoperative anti-glaucoma medications, and complications. Mean probability for each treatment was obtained using SUCRA. Ten selected articles originating from America and Europe with varying follow-up periods. SUCRA analysis shows that the combination of *Hydrus* and phacoemulsification ranks highest in reducing IOP at 92.38%, compared to the combination of *iStent* and phacoemulsification at 56.99%, and phacoemulsification only at 0.62%. The best outcomes for post-intervention BCVA ≥ 20/40 are reported in the SUCRA diagram (63.88%), as well as for the best post-intervention medication use (85.5%) and minimal complications (86.41%), which were observed in combination of *iStent* and phacoemulsification. The *Hydrus* combination intervention showed the greatest reduction in IOP, while the *iStent* combination more effective in improving visual acuity and reducing postoperative anti-glaucoma medication use and had the fewest overall postoperative complications. This study highlights that MIGS interventions, particularly *Hydrus* and *iStent* combined with phacoemulsification, offer significant benefits and show more effective compared to standalone phacoemulsification.

Keywords: *Human Medicine, MIGS, Open-angle glaucoma, Phacoemulsification.*

1. Introduction

Primary Open-Angle Glaucoma (POAG) is the most common form of glaucoma worldwide, particularly in Africa and Western countries. It is defined as a progressive optic neuropathy characterized by the loss of ganglion cells and a decrease in the visual field in eyes with open-angle gonioscopy findings, with or without elevated intraocular pressure (IOP). In cases of POAG with elevated IOP, the obstruction of aqueous outflow is thought to result from abnormalities in the extracellular matrix of the trabecular meshwork and the trabecular cells in the juxtacanalicular region or dysfunction of the endothelial cells lining the inner wall of Schlemm's canal.

Medical treatment, typically involving the stepwise use of topical anti-glaucoma medications, is the first-line approach for managing primary open-angle glaucoma. If unsuccessful and the disease progresses, alternative treatments, such as laser procedures like selective laser trabeculoplasty (SLT) or argon laser trabeculoplasty (ALT), may be considered. However, these procedures carry risks, including

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accidental damage to the retina or lens, as well as potential loss of corneal endothelial cells. Other surgical options include trabeculectomy or the implantation of a Glaucoma Drainage Device (GDD). Achieving the target intraocular pressure (IOP) in glaucoma patients can be pursued through medication, laser treatment, or filtering surgery. Due to the significant risks associated with trabeculectomy or shunt placement, newer alternatives, such as the *Hydrus* Microstent or *iStent*, have gained attention. Microinvasive Glaucoma Surgery (MIGS) offers a promising new approach to glaucoma management.

Over the past decade, the development of new surgical devices and techniques has garnered increasing interest. These techniques aim to reduce IOP with less invasive methods. However, the evolution of MIGS remains a topic of ongoing debate among experts.

Phacoemulsification presents challenges in glaucoma patients due to ocular conditions such as a history of acute glaucoma attacks, previous ocular surgeries, or trauma. Various surgical strategies exist, including phacoemulsification alone, phacoemulsification followed by glaucoma surgery, glaucoma surgery followed by phacoemulsification, or a combined approach involving both procedures performed simultaneously. However, there is no consensus on the optimal sequence of surgeries. This study aims to compare the effectiveness of two surgical devices for glaucoma, the *Hydrus* Microstent and the *iStent*, when combined with phacoemulsification versus phacoemulsification alone in patients with open-angle glaucoma. Using a network meta-analysis, the study concludes that combining phacoemulsification with either of the MIGS devices, *Hydrus* or *iStent*, is more effective in reducing intraocular pressure compared to phacoemulsification alone. Improving visual acuity, reducing the need for anti-glaucoma medications, and having fewer postoperative complications compared to phacoemulsification alone, the combination intervention with *Hydrus* showed the greatest reduction in IOP. The comparison between phacoemulsification combined with *Hydrus* and phacoemulsification combined with *iStent* demonstrated a mean IOP difference of -1.47 mmHg [95% CI -2.26; -0.69]. Furthermore, compared to phacoemulsification alone, the IOP in the group receiving phacoemulsification combined with *iStent* was reported to be lower by -0.94 mmHg [95% CI -1.53; -0.34], with a p-value <0.01. Based on the analysis, the combination of phacoemulsification with *Hydrus* provided the best IOP outcomes, followed by phacoemulsification with *iStent*, and then phacoemulsification alone.

The combination of *iStent* with phacoemulsification was superior in improving visual acuity and reducing the postoperative need for anti-glaucoma medications, with the lowest overall incidence of postoperative complications. The best BCVA outcomes (≥ 20/40) post-intervention were reported in the SUCRA diagram. Based on the analysis, the combination of *iStent* with phacoemulsification achieved the greatest reduction in postoperative medication use (63.88%), followed by phacoemulsification with *Hydrus* (48.23%), and phacoemulsification alone (37.89%).

Post-intervention medication use results from all studies approached the effect size. All studies reported significant findings with p-values <0.01. According to the SUCRA diagram, the combination of *iStent* with phacoemulsification resulted in the greatest reduction in the number of anti-glaucoma medications (85.5%), followed by *Hydrus* with phacoemulsification (54.29%), and phacoemulsification alone (10.21%). The *iStent*-phacoemulsification combination had the fewest overall postoperative complications. The most common complications were elevated IOP and reduced visual acuity. This study highlights that MIGS devices, particularly *Hydrus* and *iStent*, offer significant benefits in the management of open-angle glaucoma and present as potentially more effective treatment options compared to standalone phacoemulsification procedures.

2. Research Methods

This study is a *network* meta-analysis research, which is a quantitative statistical technique that compares several interventions simultaneously in one analysis by combining direct and indirect evidence in the study network. The subjects used in this study were patients with open-angle glaucoma and underwent various procedures Microinvasive Glaucoma Surgery Implant in combination with phacoemulsification and phacoemulsification alone. The research steps are divided into 3 stages, namely:

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literature search, data processing, and calculation. The first stage is in the form of literature search to get included studies can use the PRISMA flow. Systematic searches with pre-agreed keywords through electronic journal databases *Pubmed*, *ProQuest*, *Science Direct*, *Semantic scholar*, *Cochrane Library*, *ClinicalTrial.gov*. Research was conducted from April 2023 to July 2024.

The keywords used in this study were according to the independent variables, namely the action of implantation *of Hydrus*, *iStent* or phacoemulsification. Keywords also include bound variables, namely intraocular pressure, visual acuity, amount of anti-glaucoma drugs needed, and complications. In addition, *Medical Subject Headings* (MeSH) are used where possible to broaden the search. Literature searches are not limited by the date of publication, but filtered by published in English. The final stage of screening process was to screen the eligibility of the RCT studies using the Jadad Score. Jadad score ≥*3* will be included in this study.

Inclusion criteria were Randomised Controlled Trials (RCT) study articles with an open-angle glaucoma patient population receiving *Hydrus*, *iStent* combined with phacoemulsification or phacoemulsification alone. Exclusion criteria included case reports, case series, reviews, metaanalysis, editorials, expert opinions and similar articles using secondary sources, duplicate articles, studies where the full text of the study could not be retrieved.

The data in this study will be presented in basic characteristics, visualized were the author's name, year of publication, study design, study location, number of samples, diagnosis, intervention procedure, and follow-up time, IOP, visual acuity, drug use and complications. Statistical analysis was carried out with *MetaInsight* V3.1.11 software. Results will be presented using *mean differences* (MDs) with a 95% *confidence interval*. To assess the ranking of each intervention, the SUCRA (*Surface Under The Cumulative Ranking*) *probability method is used*, namely *P-score*.

This study used a consistency test to assess the extent to which the results of the different trials included in the analysis showed uniformity or similarity of effect. In the context of meta-analysis, consistency is important because highly incons*iStent* results may indicate significant heterogeneity, which affects the validity and generalisability of the pooled results. Consistency testing is important to increase confidence in the results of a meta-analysis.

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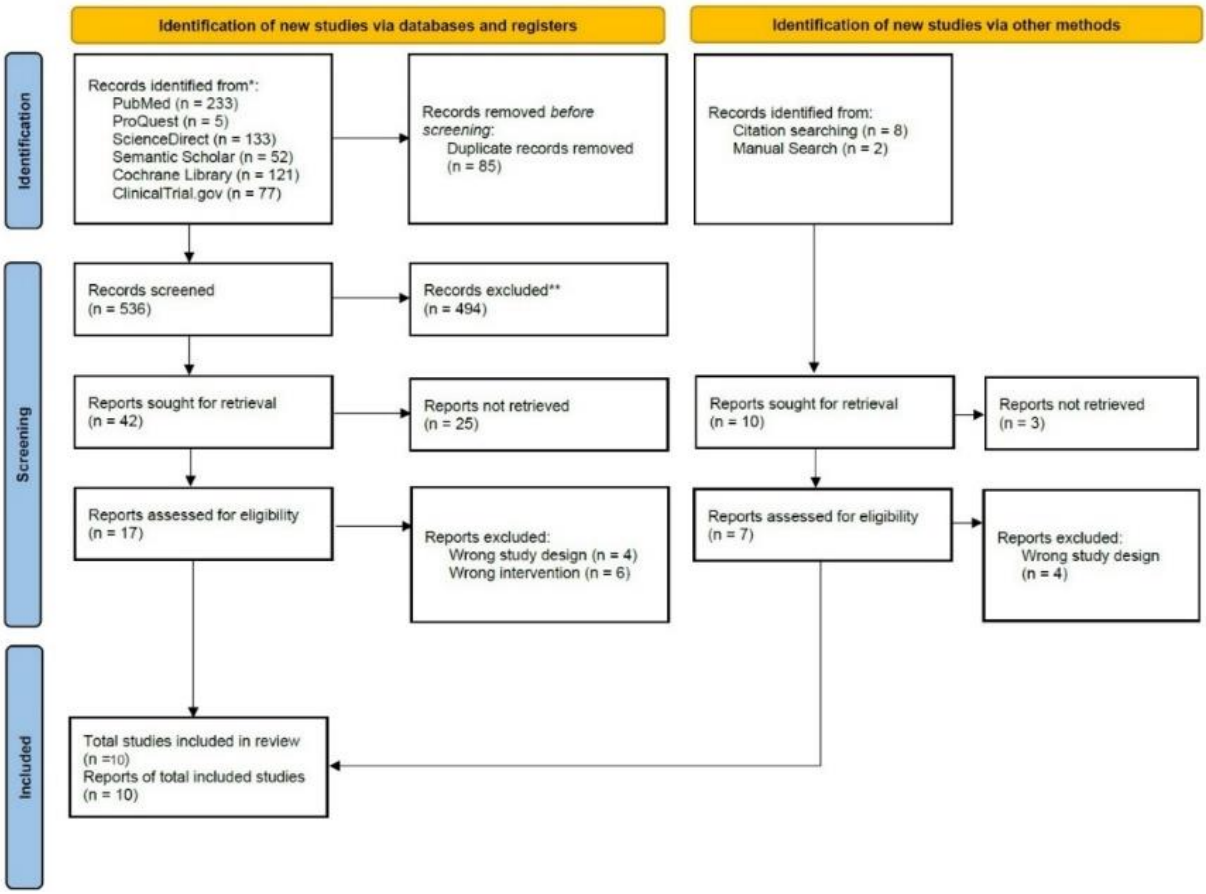

Figure 1.
PRISMA Flowchart Diagram of search and screening.

3. Research Result

A search in databases resulted in 621 studies matching the search keywords. 8 studies were obtained from citation search, and 2 studies from manual search. After duplicate removal, 536 studies were examined and irrelevant studies, such as case reports, literature reviews, and experimental studies were removed. A total of 17 studies were screened with eligibility criteria and 7 studies from the citation search were then thoroughly reviewed. A total of 25 studies were not randomised controlled trials (RCTs), did not include the intervention of interest or did not include the outcome of interest. From the selection, 10 studies met the criteria and were used in the network meta-analysis.

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Table 1.
Jadad score for research bias.

Study	Was the study described as randomized?	Was the method of randomization appropriate?	Was the study described as blinded?	Was the method of blinding appropriate?	Was there a description of withdrawals and dropouts	Total
Fea *et al.*, 2010	1	1	1	1	1	*5*
Fernandez-Barrientos *et al.*, 2010	1	1	0	0	1	*3*
Craven, *et al.*, 2012	1	1	0	0	1	*3*
Wells, *et al.*, 2014	1	1	0	0	1	*3*
Fea *et al.*, 2015	1	1	1	1	1	*5*
Pfeiffer, *et al.*, 2015	1	1	0	0	1	*3*
Samuelson *et al.*, 2018	1	1	0	0	1	*3*
Laspas *et al.*, 2019	1	1	0	0	1	*3*
Samuelson *et al.*, 2019	1	1	0	0	1	*3*
CDMA, 2024	1	1	0	0	1	*3*

The risk of research bias for each article is shown in Table 1. All articles had a good Jadad score with values of 3-5 and used randomisation. Double blind was only found in two articles. All studies included in this review were rated as high quality or low risk of bias.

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Table 2.
Characteristics of the studies used in the research.

Author (Year)	Study design	Title	Location	Intervention vs. control	Sample	*Follow-up* (Month)
Fea *et al.*, 2010	RCT	Phacoemulsification versus phacoemulsification with micro-bypass stent implantation in primary open-angle glaucoma: randomized double-masked clinical trial	Italy	Phacoemulsification + *iStent*s vs. Phacoemulsification	Intervention: 12 Control: 21	1, 2, 3, 6, 9, 12, 15
Fernandez-Barrientos *et al.*, 2010	RCT	Fluorophotometric Study of the Effect of the Glaukos Trabecular Microbypass Stent on Aqueous Humor Dynamics	Spain	Phacoemulsification + *iStent*s vs. Phacoemulsification	Intervention: 17 Control: 16	1, 6, 12
Craven, *et al.*, 2012	RCT	Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: Two-year follow-up	USA	Phacoemulsification + *iStent*s vs. Phacoemulsification	Intervention: 132 Control: 115	24
Wells, *et al.*, 2014	RCT	Safety and Efficacy of the GTS400 Stent in Conjunction With Cataract	Not Available	Phacoemulsification + *iStent*s vs. Phacoemulsification	Intervention: 27 Control: 17	12
Fea *et al.*, 2015	RCT	Clinical Study Micro-Bypass Implantation for Primary Open-Angle Glaucoma Combined with Phacoemulsification: 4-Year Follow-Up	Italy	Phacoemulsification + *iStent*s vs. Phacoemulsification	Intervention: 12 Control: 21	64
Pfeiffer, *et al.*, 2015	RCT	A Randomized Trial of a Schlemm's Canal Microstent with Phacoemulsification for Reducing Intraocular Pressure in Open-Angle Glaucoma	Germany, Spain, Italy, Netherlands, USA	Phacoemulsification + *Hydrus* vs. Phacoemulsification	Intervention: 47 Control: 43	1, 3, 6, 12, 18, 24

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Author (Year)	Study design	Title	Location	Intervention vs. control	Sample	*Follow-up* (Month)
Samuelson *et al.*, 2018	RCT	A Schlemm Canal Microstent for Intraocular Pressure Reduction in Primary Open-Angle Glaucoma and Cataract The HORIZON Study	USA	Phacoemulsification + *Hydrus* vs. Phacoemulsification	Intervention: 369 Control: 187	1, 6, 12, 24
Laspas *et al.*, 2019	RCT	Three-Year Results of *Hydrus* Microstent with Phacoemulsification	Germany, Spain, Italy, Netherlands, USA	Phacoemulsification + *Hydrus* vs. Phacoemulsification	Intervention: 45 Control: 43	36
Samuelson *et al.*, 2019	RCT	Prospective, Randomized, Controlled Pivotal Trial of an Ab Interno Implanted Trabecular Micro-Bypass in Primary Open-Angle Glaucoma and Cataract	USA	Phacoemulsification + *iStent*s vs. Phacoemulsification	Intervention: 387 Control: 118	1, 3, 6, 11, 12, 18, 23, 24
CDMA, 2024	RCT	Comparing *Hydrus* Microstent I to the *iStent* for Lowering IOP in Glaucoma Patients Undergoing Cataract Surgery	USA	*Hydrus* + Phacoemulsification vs. *iStent*s + Phacoemulsification	*Hydrus* + Phacoemulsification: 154 *iStent*s + Phacoemulsification: 152	12, 24

Table 3.

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Baseline characteristics of age, IOP, medication use, and BCVA used in the study.

Article (Year)	Intervensi	Age (Year)	Baseline		
			IOP	Medication use	BCVA
Fea *et al.*. (2010)	Phacoemulsification	64.9 ± 3.1	17.3 ± 3.0	1.9 ± 0.7	-
	iStent + Phacoemulsification	64.5 ± 3.4	17.9 ± 2.6	2.0 ± 0.9	
Fernandez-barrientos *et al.*. (2010)	Phacoemulsification	76.7 ± 5.8	23.6 ± 1.5	1.2 ± 0.7	-
	iStent + Phacoemulsification	75.2 ± 7.2	24.2 ± 1.8	1.1 ± 0.5	
Craven. *et al.*. (2012)	Phacoemulsification	-	17.8 ± 3.3	-	-
	iStent + Phacoemulsification	-	17.1 ± 2.9	-	
Wells. *et al.*. (2014)	Phacoemulsification	-	-	-	-
	iStent + Phacoemulsification	-	-	-	
Fea *et al.*. (2015)	Phacoemulsification	-	16.7 ± 3	1.8 ± 0.7	-
	iStent + Phacoemulsification	-	17.8 ± 2.7	1.9 ± 0.9	-
Pfeiffer. *et al.*. (2015)	Phacoemulsification	71.5± 6.9	19.2 ± 4.7	2.0 ± 1.1	20/40 (20/16-20/400)
	Hydrus + Phacoemulsification	72.8 ± 6.6	16.9 ± 3.3	2.0 ± 1.0	20/40 (20/13-20/16)
Samuelson *et al.*. (2018)	Phacoemulsification	71.2 ± 7.6	18.1 ± 3.1	0.7 ± 0.9	20/40(20/138-20/16)
	Hydrus + Phacoemulsification	71.1 ± 7.9	17.9 ± 3.1	0.3 ± 0.8	20/40 (20/240 – 20/14)
Laspas *et al.*. (2019)	Phacoemulsification	71.5± 6.9	19.2 ± 4.7	1.0 ± 1.0	-
	Hydrus + Phacoemulsification	72.8 ± 6.6	16.9 ± 3.3	0.5 ± 1.0	
Samuelson *et al.*. (2019)	Phacoemulsification	70.1	17.54 ± 2.78	1.5 ± 0.7	20/40
	iStent + Phacoemulsification	69.0	17.54 ± 2.9	1.6 ± 0.81	20/40
CDMA. (2024)	*iStent* + Phacoemulsification	71.5(7.5)	-	-	-
	Hydrus + Phacoemulsification	72.5(7.2)	-	-	

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3.1. Intaocular Pressure

There were six studies that compared the treatment of OAG using *iStent implantation* in combination with phacoemulsification and the treatment of OAG with phacoemulsification alone. Fernandez-Barrientos *et al.*, 2010 reported that the phacoemulsification group alone had an initial IOP value of 23.6 ± 1.5 with drug use 1.2 ± 0.7. Meanwhile, a study by Samuelson *et al.* (2018) showed that the combination of *Hydrus* and phacoemulsification had an initial IOP value of 17.9 ± 3.1 with lower drug use, i.e. 0.3 ± 0.8, compared to phacoemulsification alone which had an initial IOP value of 18.1 ± 3.1 with drug use of 0.7 ± 0.9.

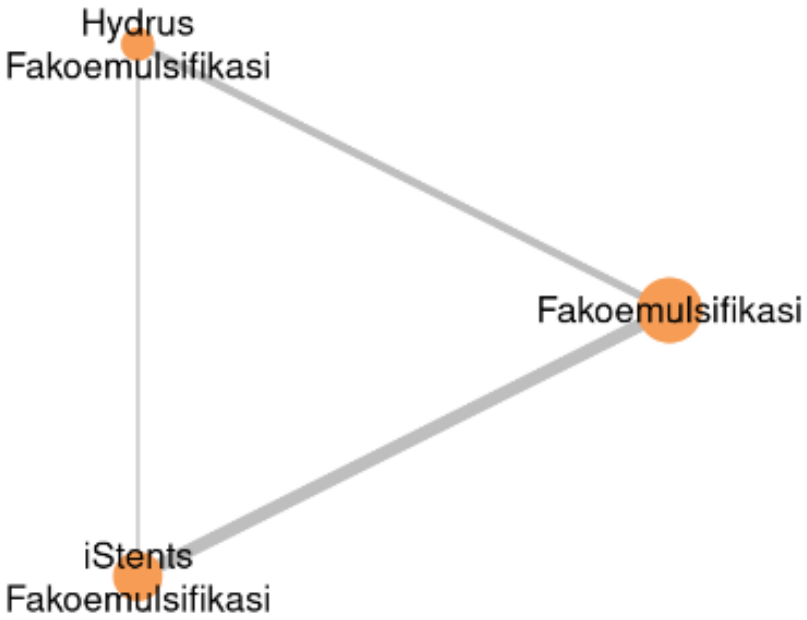

Figure 2.
Network plot direct comparison of IOP.

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Table 4.
Average intra-ocular pressure after *Follow-up*.

Article (Year)	IOP (mmHg)		
	Phacoemulsification	***iStents* + Phacoemulsification**	***Hydrus* + Phacoemulsification**
Fea *et al.*, (2010)	15,7 ± 1,1	14,8 ± 1,2	-
Fernandez-Barrientos *et al.*, (2010)	19,8 ± 2,3	17,6 ± 2,8	-
Craven, *et al.*, (2012)	17,8 ± 3,3	17,1 ± 2,9	-
Fea *et al.* (2015)	17,0 ± 2,5	15,9 ± 2,3	-
Pfeiffer, *et al.*, (2015)	19,2 ± 4,7	-	16,9 ± 3,3
Samuelson *et al.*, (2018)	17,3 ± 4,0	-	16,8 ± 3,2
Laspas *et al.*, (2019)	20,6 ± 5,3	-	18,3 ± 4,0
Samuelson *et al.*, (2019)	12,14 ±3,7	10,99 ± 4,0	-
CDMA, (2024)	-	18,1 ± 4,9	16,9 ± 4,5

IOP at post-intervention observation (Table 4) showed a decrease when compared to baseline IOP values (Table 3) for all treatments, either phacoemulsification alone or in combination with *iStent* or *Hydrus*. Combination of *Hydrus* with phacoemulsification could reduce IOP to 16.8 ± 3.2 mmHg. Pfeiffer *et al.* (2015) also noted that the IOP in phacoemulsification alone was 19.2 ± 4.7 mmHg, while the combination of *Hydrus* with phacoemulsification could decrease to 16.9 ± 3.3 mmHg.

It was found the comparison between the combination of *Hydrus* with phacoemulsification and *iStents with phacoemulsification* showed a mean decrease in IOP of -1.47 mmHg [95% CI -2.26; -0.69] which was lower in the combination group *of Hydrus* with phacoemulsification combination group. IOP in the combination group *of iStents* with phacoemulsification was reported to be lower by -0.94 mmHg [CI 95% -1,53; -0,34].

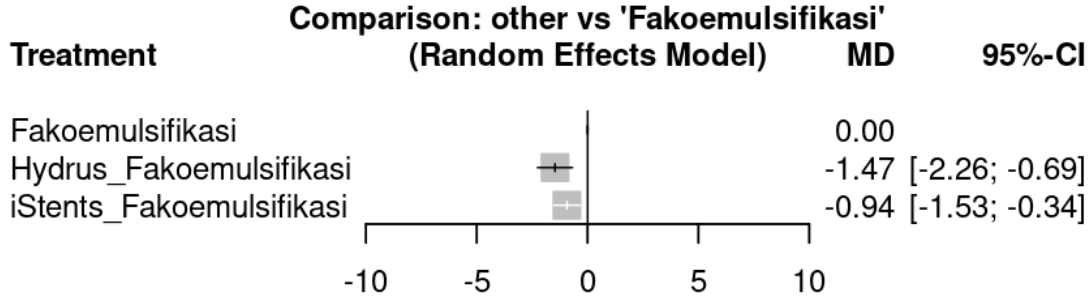

Figure 3.
Forest plot direct and indirect comparison of IOP.

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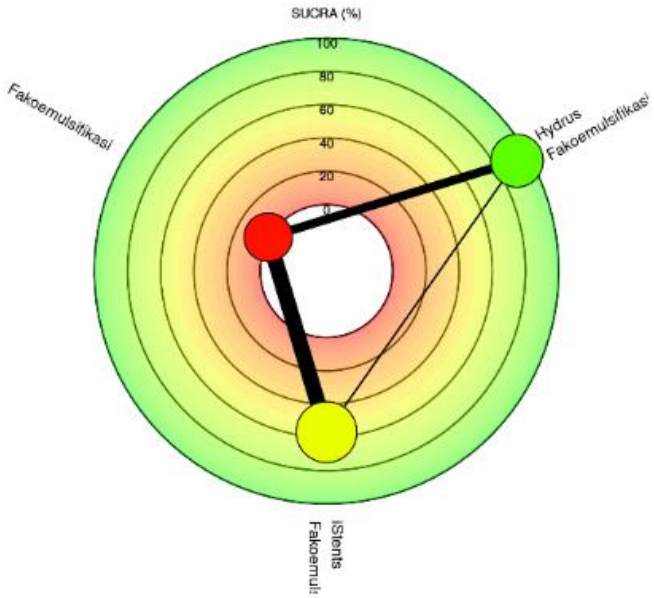

Figure 4.
SUCRA IOP diagram.

Table 5.
Treatment Rank SUCRA IOP.

Therapy	Rank 1	Rank 2	Rank 3	SUCRA
Phacheemulsification	0.00	0.01	0.99	0.62
Hydrus + Phacheemulsification	0.85	0.15	0.00	92.38
iStents + Phacheemulsification	0.15	0.84	0.01	56.99

The order of selection of interventions with the best IOP outcomes is reported in the SUCRA diagram (Figure 4). Based on the analysis, the combination of *Hydrus* with phacoemulsification gave the best IOP results, followed by the combination of phacoemulsification with *iStent*, and phacoemulsification alone.

3.2. Visual Acuity

There were three studies that reported *best corrected visual acuity* (BCVA) parameter for the treatment of OAG using a combination of *Hydrus and* phacoemulsification, a combination of *iStents* with phacoemulsification, and phacoemulsification alone.

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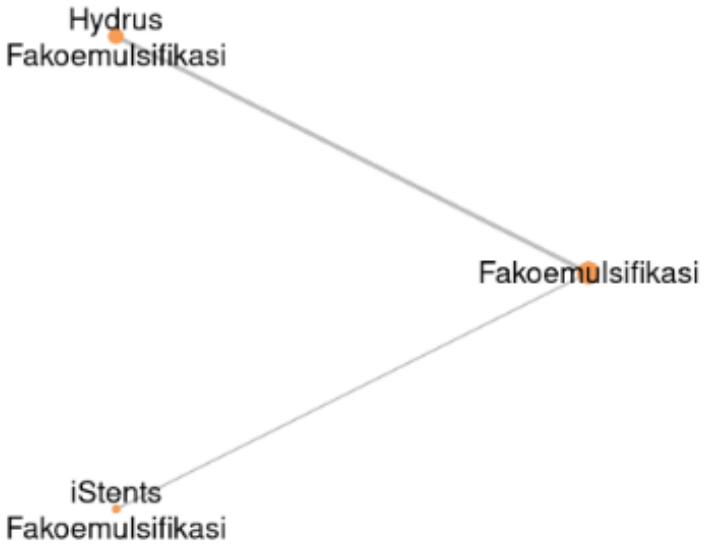

Figure 5.
Network Plot Direct Comparison of BCVA ≥ 20/40.

Samuelson *et al.*, study, (2019) revealed the combination of *iStent* with phacoemulsification successfully improved visual acuity in 383 out of 387 patients (99%). For the combination of *Hydrus* with phacoemulsification, Pfeiffer *et al.*, (2015) noted that 95.7% of patients (45 out of 47 patients) achieved BCVA ≥ 20/40. These findings show that both *iStents and Hydrus* not only support the effectiveness of phacoemulsification, but can also help patients achieve high visual acuity after surgery.

Table 6.
Number of patients who experienced an increase in BCVA ≥ 20/40 Post *Follow-up*.

Article (Year)	BCVA ≥ 20/40		
	Phaco	Phaco + *iStents*	Phaco + *Hydrus*
Pfeiffer, *et al.*, (2015)	39/43	-	45/47
Samuelson *et al.* (2018)	176/187	-	345/369
Samuelson *et al.* (2019)	116/118	383/387	-

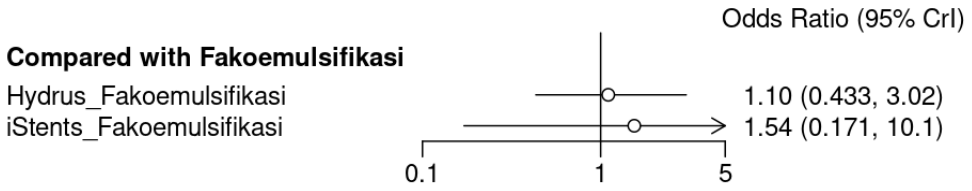

Figure 6.
Forest plot Direct and Indirect Comparison of BCVA Increase ≥ 20/40 Post-intervention.

The sequence of BCVA outcomes ≥ 20/40 best post-intervention is reported in the SUCRA diagram (Figure 5.11). Based on the analysis, the combination of *iStent* with phacoemulsification gave the best bcva results (63.88%), followed by *Hydrus* combination with phacoemulsification (48.23%), and phacoemulsification alone (37.89%).

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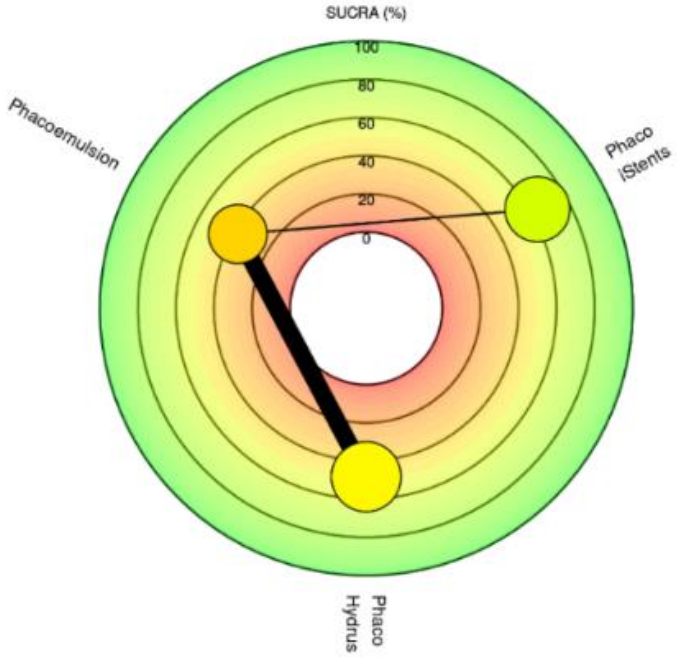

Figure 7.
SUCRA BCVA ≥ 20/40 Post-intervention.

Table 7.
Treatment rank SUCRA BCVA ≥ 20/40.

Therapy	Rank 1	Rank 2	Rank 3	SUCRA
Phacheemulsification	0.14	0.48	0.38	37.89
Hydrus + Phacheemulsification	0.29	0.39	0.32	48.23
iStents + Phacheemulsification	0.57	0.13	0.29	63.88

3.3. Number of Anti-Glaucoma Medication

Nine of the ten studies included in this network meta-analysis discussed the use of post-intervention medication as one of the parameters. The direct comparative representation is visualized in Figure 8.

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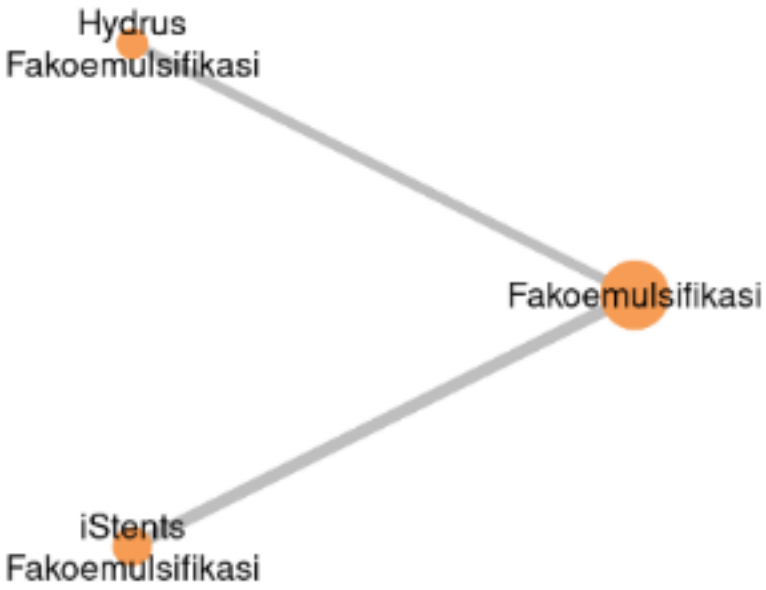

Figure 8.
Network plot direct comparison of the use of anti-glaucoma medication post-intervention.

The use of post-glaucoma medication was found to be lower in each of the combination groups (Table 8). The study by Fea *et al*., (2010) showed that medication use was 1.3 ± 1.0 in patients who underwent phacoemulsification alone, whereas medication use was lower at 0.4 ± 0.7 in patients who underwent the combination of *iStent* and phacoemulsification. Furthermore, Fernandez-Barrientos *et al*., (2010) showed that the use of medication in phacoemulsification alone was 0.7 ± 1.0, while in the combination group *of iStents* with phacoemulsification was 0.00 ± 0, where patients stopped taking anti-glaucoma drugs after intervention.

Samuelson *et al*., (2018) reported that the drug use in phacoemulsification alone was 0.7 ± 0.9, while the combination of *Hydrus* with phacoemulsification was lower with an average drug use of 0.3 ± 0.8.

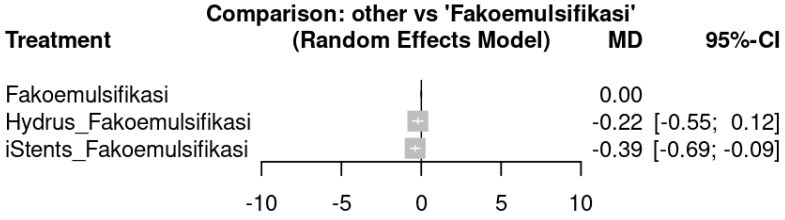

Figure 9.
Forest plot direct and indirect comparison of post-intervention drug use.

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Table 8.
Average use of anti-glaucoma drugs post-follow-up.

Article	Drug use		
	Phacoemulsification	***iStent* + Phacoemulsification**	***Hydrus* + Phacoemulsification**
Fea *et al.*, (2010)	1,3 ± 1,0	0,4 ± 0,7	-
Fernandez-Barrientos *et al.*, (2010)	0,7 ± 1,0	0,00 ± 0	-
Craven, *et al.*, (2012)	0,5 ± 0,7	0,3 ± 0,6	-
Wells, *et al.*, (2014)	0,9 ± 0,7		0,4 ± 0,8
Fea *et al.*, (2015)	1,0 ± 1,0	0,4 ± 0,7	-
Pfeiffer, *et al.*, (2015)	1,0 ± 1,0	-	0,5 ± 1,0
Samuelson *et al.*, (2018)	0,7 ± 0,9	-	0,3 ± 0,8
Laspas *et al.*, (2019)	0,7 ± 1,0	-	1,3 ± 1,0
Samuelson *et al.*, (2019)	0,8 ± 1,0	0,4 ± 0,8	-

The use of anti-glaucoma medications at the post-intervention follow-up (Table 8) decreased compared to the use of anti-glaucoma medications at baseline (Table 3) for all treatments either phacoemulsification, *iStent* or *Hydrus*. A higher decrease in the use of anti-glaucoma medications was found in the *iStent* combination group with phacoemulsification compared to the *Hydrus* combination group with phacoemulsification.

Based on SUCRA analysis, the combination of *iStent* with phacoemulsification gave the best post-intervention drug use results (85.5%), followed by the combination of *Hydrus* with phacoemulsification (54.29%), and phacoemulsification alone (10,21%).

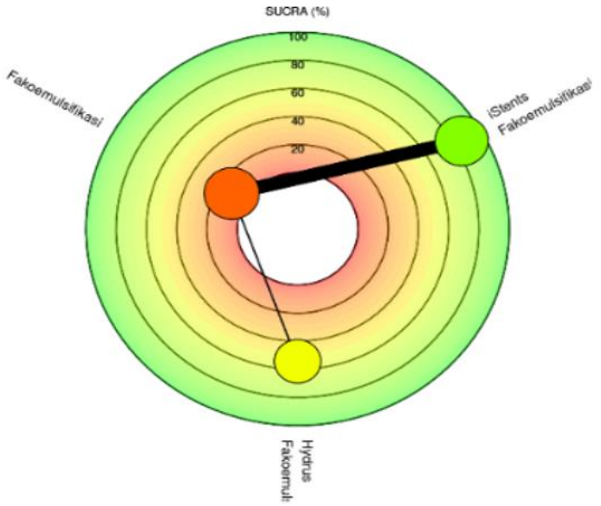

Figure 10.
SUCRA diagram of medications use.

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Table 9.
Treatment rank SUCRA drug use.

Therapy	Rank 1	Rank 2	Rank 3	SUCRA
Phacheemulsification	0.01	0.19	0.80	10.21
Hydrus + Phacheemulsification	0.26	0.54	0.17	54.29
iStents + Phacheemulsification	0.74	0.24	0.03	85.50

3.4. Postoperative Complications

Studies of complications following phacoemulsification, whether performed alone or in combination with devices such as *Hydrus* and *iStents*, show mixed results. Some studies report no complications at all (Fea *et al*., 2015), while others report complications such as increased IOP, decreased visual acuity and conjunctivitis. In phacoemulsification alone, the most common complications were an increase in IOP of up to 52,9% (Wells *et al*., 2014) and a decrease in visual acuity of up to 8,9% (Samuelson *et al*., 2019). In the CDMA study, 2024 the combination of *Hydrus* with phacoemulsification had a lower complication rate, such as an increase in IOP of only 3,2%-10%, but there was still a risk of other complications such as iritis of 5,1%. The combination of *iStent* and phacoemulsification generally showed fewer complications than *Hydrus*, such as a 7,2% increase in IOP and a 0,7% decrease in visual acuity. According to Samuelson *et al*., 2019, phacoemulsification alone showed a much higher complication rate (34,1%), with a sharp decrease in visual acuity of 8,9%. Furthermore, 9,8% of posterior capsule opacification and 8,9% of corneal oedema were reported.

In some cases, complications require additional interventions, such as administration of anti-glaucoma medication or reoperation. The combination of phacoemulsification with additional devices tends to be safer than phacoemulsification procedures alone, with complication rates varying between methods and studies.

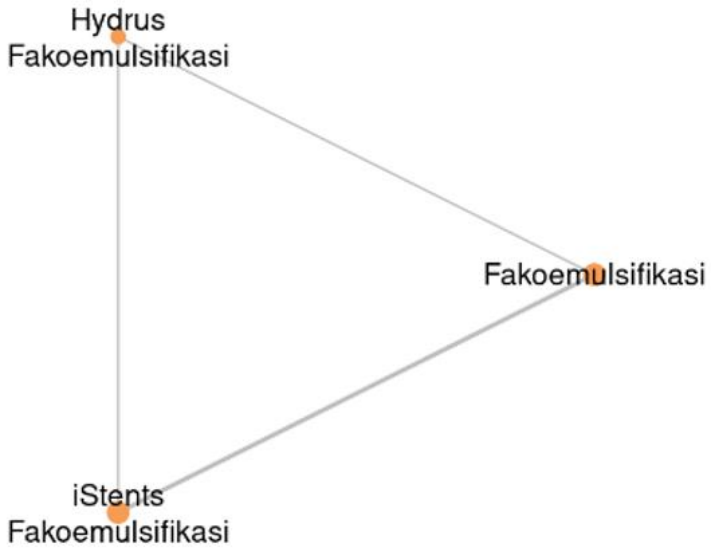

Figure 11.
Network plot direct comparison of overall complications post-intervention.

A total of five studies included in this meta-analysis metwork addressed overall complications as one of the parameters. A direct comparative representation is depicted in Figure 11.

The meta-analysis showed the results of the OR model from each study. In the study of Samuelson *et al*., 2018, the overall complication of the combination *of Hydrus* with phacoemulsification compared to

phacoemulsification alone showed an OR of 2.74 [95% CI 1.69, 4.44]. Furthermore, the combination of *iStent* with phacoemulsification compared to phacoemulsification alone showed a smaller risk of complications, with an OR of 0.59 [95% CI; 0.33, 1.03] in Samuelson *et al*., 2019, and 0.52 [95% CI 0.14, 1.89] in Wells, *et al.*, 2014. In CDMA study (2014), *iStents* had a lower risk of complications, with an OR of 0.64 [95% CI 0.32, 1.25].

Based on the analysis, the combination *of iStent* with phacoemulsification gave the most overall complication results (86.41%).

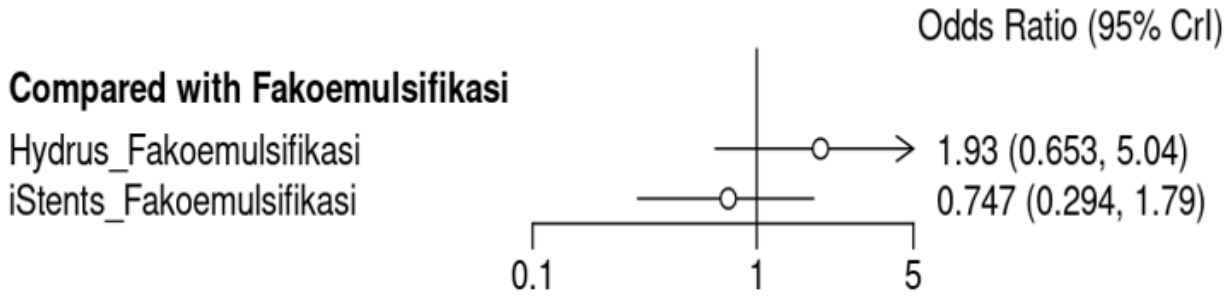

Figure 12.
Forest plot Direct and indirect comparison of overall complications post-intervention.

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Table 10.
Full description of complications in each study.

		Total	**K1**	**K2**	**K3**	**K4**	**K5**	**K6**	**K7**	**K8**	**K9**	**K10**	**K11**	**K12**	K13
Wells. *et al.*. 2014	Phacoemulsification	70.6%	52.9%	11.8%	11.8%	0.0%	5.9%	5.9%	5.9%	11.8%	5.9%				
	Phacoemulsification + *iStent*	55.6%	11.1%	0.0%	11.1%	7.4%	14.8%	3.7%	3.7%	3.7%	0.0%				
CDMA. 2014	*Hydrus* + Phacoemulsification	15.6%	3.2%	0.0%								1.3%	0.0%		
	Phacoemulsification + *iStent*	10.5%	7.2%	0.7%								2.6%	0.6%		
Pffeifer *et al.*. 2015	Phacoemulsification		4.0%	6.0%							2.0%			4.0%	2.0%
	Hydrus + Phacoemulsification		4.0%	0.0%							0.0%			2.0%	12.0%
Samuelson *et al.*. 2018	Phacoemulsification	12.8%		0.5%	7.5%	1.6%						0.5%		0.0%	
	Hydrus + Phacoemulsification	28.7%		0.0%	7.3%	5.1%						0.0%		0.3%	
Samuelson *et al.*. 2019	Phacoemulsification	34.1%		8.9%			9.8%							8.9%	
	Phacoemulsification + *iStent*	23.3%		6.0%			6.0%							7.8%	

Note: Total: Overall complications; K1: increased IOP, K2: sharp decrease in vision, K3: conjunctivitis, K4: Iritis, K5: posterior capsule opalysis; K6: Punctate corneal staining, K7: Superficial punctate keratitis, K8: Pain, K9: Retinal detachment; K10: Uncontrolled glaucoma, K11: Macular degeneration, K12: Corneal edema, K13: Focal peripheralanterior synechiae.

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3.5. Elevated IOP

Elevated IOP and Decrease in Visual Acuity are the two most frequent complications. This network meta-analysis involving three studies with a total of 450 patients evaluated post-intervention complications, elevated IOP as the main complication. Comparisons were made between the combination of *iStent* and phacoemulsification with phacoemulsification alone, the combination of *Hydrus* and phacoemulsification with phacoemulsification alone, and the combination of *Hydrus* with *iStent* combination with phacoemulsification. Results showed that the combination of *Hydrus* with phacoemulsification had an overall complication risk of 23.2% [CI 95% 1.73-39.5%], with an OR of 1.00 [CI 95% 0.14-7.39] and an IOP elevation rate of 70.4%. The combination of *iStent* with phacoemulsification showed an overall complication risk of 25.8% [CI 95% 1.99-34.1%], with an OR of 0.11 [CI 95% 0.02-0.51] according to Wells *et al*., 2014, although other studies reported a higher complication risk compared to *Hydrus*, with an OR of 2.32 [CI 95% 0.79-6.86].

Based on the analysis, *Hydrus* combined with phacoemulsification had a complication risk of 0.232 [95% CI 0.0173; 0.395]. On the other hand, *iStent* combined with phacoemulsification showed an OR of 0.258 [95% CI 0.0199; 0.341]. *Hydrus* is better to be the main therapy to avoid the complication of elevated IOP.

3.6. Decrease in Visual Acuity

A network meta-analysis of five studies with a total of 1245 patients evaluated postoperative complications, with decreased visual acuity being the second most common complication after increased intraocular pressure (IOP). The study compared the risk of complications between the combination of *iStent* and phacoemulsification with phacoemulsification alone, the combination of *Hydrus* and phacoemulsification with phacoemulsification alone, and the combination of *Hydrus* and *iStent*.

The results of the network meta analysis showed that the combination of *Hydrus* with phacoemulsification had a lower risk of visual loss than phacoemulsification alone, with ORs of 0.13 [95% CI 0.01-2.67] (Pffeifer *et al*, 2015) and 0.17 [95% CI 0.01-4.15] (Samuelson *et al*, 2018). The combination of *iStent* and phacoemulsification also showed a lower risk than phacoemulsification alone, with OR 0.11 [95% CI 0.01-2.50] (Wells *et al*., 2014) and 0.65 [95% CI 0.24-1.75] (Samuelson *et al*., 2019). However, the CDMA study (2014) reported that *iStent* had a higher risk of this complication than *Hydrus*, with an OR of 3.06 [CI 95% 0.12-75.69].

Overall, the combination of *Hydrus* with phacoemulsification had the lowest risk of visual loss, followed by the combination of *iStent* with phacoemulsification, and then phacoemulsification alone.

4. Discussion

Minimally Invasive Glaucoma Surgery (MIGS) is a new surgical procedure for the treatment of glaucoma. The goal of this procedure is to safely and effectively lower IOP with minimal trauma to the eye and fewer complications. The way *iStent* works is by letting *the aqueous humor* flow directly from the anterior chamber into the Schlemm canal through the trabecular meshwork. *The iStent* is safe and an effective tool in the management of open-angle glaucoma (Shalaby *et al*., 2021). *Hydrus* Microstent is an intracanalicular scaffold that reduces IOP for the management of glaucoma. This can be done by inserting *hydrus* through the trabecular meshwork into the Schlemm canal which is usually done in conjunction with cataract surgery (Pfeiffer *et al*., 2015).

4.1. Comparison of Hydrus Implantation, IStent Combination Phacoemulsification Compared to Phacoemulsification Alone based on Intraocular Pressure

In this study, the baseline initial IOP for the three groups between the combination of *Hydrus* and phacoemulsification, the combination of *iStent* with phacoemulsification and phacoemulsification alone did not show any statistically significant difference, but in the post-follow-up observation there was a significant decrease in IOP between the combination group or phacoemulsification only. These results are supported by the results of other studies that show that postoperative follow-up carried out 12

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months post-intervention, intraocular pressure was lower in the combination group of *Hydrus* with phacoemulsification (Manasses and Au, 2016).

At observation after 2 years, it was found that the IOP in *Hydrus* intervention group was lower than phacoemulsification group and the results showed a statistically significant difference (16.9 ± 3.3 mmHg with 19.2 ± 4.7 mmHg; *P= 0.0093*) (Pfeiffer *et al.* 2015). Obtained *Hydrus* in combination with phacoemulsification is better in lowering IOP (Hu *et al.*, 2022).

The results of *network meta analysis* showed a better decrease in IOP in the combination of *Hydrus* with phacoemulsification, followed by the combination of *iStent* with phacoemulsification, and phacoemulsification alone. The combination of *Hydrus* with phacoemulsification is known to produce a lower IOP of -1.47 mmHg compared to phacoemulsification alone [CI 95% -2.26; -0.69]. Furthermore, the combination with *iStent* can result in lower postoperative IOP compared to phacoemulsification alone with a difference of -0.94 [CI 95% -1,53; -0,34] mmHg.

4.2. Comparison of Hydrus Implantation, IStent Combination Phacoemulsification Compared to Phacoemulsification Alone based on Visual Acuity

There were three studies that reported the proportion of patients who had a BCVA ≥ 20/40. Network meta-analysis showed that the combination *of iStent* with phacoemulsification showed a better proportion of BCVA ≥ 20/40 compared to the other two interventions, with OR of 1.51 (95% CI 0.169; 10.30). Furthermore, the combination of *Hydrus* with phacoemulsification also showed better results than phacoemulsification alone, with OR of 1.10 (95% CI 0.434; 3.02). However, SUCRA results showed a modest difference, with results of 63.88%, 48.23%, and 37.89% for the *iStent* combination with phacoemulsification, *Hydrus* combination with phacoemulsification, and phacoemulsification alone, respectively.

Post-implantation BCVA stability is critical for patient satisfaction and quality of life. The mechanism of action of *Hydrus* and *iStent*s to lower IOP directly affects BCVA by increasing aqueous humour outflow and reducing IOP. A steady decrease in IOP is essential to prevent progressive damage to the optic nerve, which is the main cause of vision loss in glaucoma. (Jabłońska J, *et al*., 2023).

4.3. Comparison of Hydrus Implantation, IStent Combination Phacoemulsification Compared to Phacoemulsification Alone based on the Number of Anti-glaucoma Medication.

The use of postoperative medication in the group that underwent phacoemulsification ranged from 0.5 to 1.3 medication per day. Fea *et al*., (2010) reported an average drug use of 1.3 ± 1.0, while Craven *et al*., (2012) reported an average of 0.5 ± 0.7. In the group that underwent *iStent* in combination with phacoemulsification, there was a significant decrease in medication use. Fernandez-Barrientos *et al*., (2010) even reported the absence of medication use (0.00 ± 0), which showed the effectiveness of *iStents* in reducing medication needs. The use of *Hydrus* in combination with phacoemulsification has also shown favorable results. Pfeiffer *et al*., (2015) and Samuelson *et al*., (2018) reported a decrease in postoperative medication use to 0.5 ± 1.0 and 0.3 ± 0.8, respectively.

The results of the reduction of IOP and the consumption of more effective anti-glaucoma medication are described in the literature, *Hydrus* is designed to cover about 90 degrees of the Schlemm canal, thus offering a larger area compared to *iStent*, which only penetrates about 1 mm into the Schlemm canal. This large coverage area allows *Hydrus* to create a more effective bypass on the trabecular mesh, thereby improving fluid drainage from the eye. As a result, the resistance within the canal is reduced more efficiently, resulting in a lower IOP, in line with its design goals for better management of glaucoma (Ahmed *et al*., 2019). The *iStent*, combined with phacoemulsification, can provide sustained IOP reduction without relying on pharmacological mechanisms. By addressing key obstacles in the trabecular meshwork, the eyeball pressure becomes more physiological, often reducing or even eliminating the need for drug therapy (Weinreb *et al*., 2014).

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4.4. Comparison of Hydrus Implantation, IStent Combination Phacoemulsification Compared to Phacoemulsification Alone based on Post-Intervention Complications

This study assessed postoperative complications in phacoemulsification surgeries, conducted either independently or in conjunction with adjunct devices like iStent and Hydrus. Reported complication rates ranging from 10.55% to over 70.6%.

Results showed that the combination of *Hydrus* with phacoemulsification had a higher overall complication rate than the combination of *iStent* with phacoemulsification or phacoemulsification alone. The complexity factor of the *Hydrus* implantation technique, which requires more careful placement in Schlemm's canal, contributes to higher intraoperative complications compared to the simpler and easier-to-install *iStent* (Jabłońska J, *et al*., 2023).

Elevated IOP is the most commonly reported complication. Based on analysis, the combination of *Hydrus* or *iStent* with phacoemulsification has less risk of IOP elevation than phacoemulsification alone. Canal obstruction due to implant malposition or haemorrhage (hyphema) is frequently reported as a cause of IOP elevation, with the prevalence of obstruction reaching 4.3% in *iStents* (Wellik *et al*., 2015; Kim *et al*., 2023).

Decrease in visual acuity was the second most common complication, with less likelihood in the combination of *Hydrus* and phacoemulsification than the combination of *iStent* and phacoemulsification, or phacoemulsification alone. However, heterogeneity in the definition of visual impairment between studies, such as changes in more than one or two BCVA lines, resulted in variations in the results. Factors such as vitreomacular traction and cystoid macular edema are also causes of postoperative visual impairment (Lenzhofer *et al*., 2019).

The results suggest the need for further evaluation to understand the factors that influence complications and the effectiveness of the intervention. The choice of surgical technique should be tailored to the patient's condition and surgeon's preference to minimise the risk of complications.

4.5. Comparison of Hydrus Implantation, IStent Combination Phacoemulsification Compared to Phacoemulsification Alone based on Clinical Recommendation

The choice between *Hydrus* and *iStent* in the treatment of open-angle glaucoma is based on efficacy, safety and patient-specific factors. Studies have shown that both devices are effective in reducing intraocular pressure (IOP) and the need for glaucoma medications, with *Hydrus* providing a higher proportion of drug-free patients than *iStent* (Hu *et al*, 2022; Sharma *et al*, 2024). However, another study showed that the combination of *iStent* and phacoemulsification provided a more significant reduction in glaucoma medication requirements (Vizzari & Ceruti, 2024).

The complication profile showed that *Hydrus* had a higher incidence of hyphema and device occlusion compared to *iStent*. For example, the incidence of postoperative hyphema in *Hydrus* patients was 8% compared to no reported cases with the *iStent* (Chee *et al*, 2023). This may be due to the *Hydrus* design, which requires more complex implantation techniques, increasing the risk of intra-operative complications (Jabłońska *et al*, 2023). However, *Hydrus* provides better outcomes in patients with high preoperative IOP, particularly in mild to moderate glaucoma (Fea *et al*, 2023).

The *iStent* has a lower complication profile, making it a safer option for patients at higher risk of complications (Sharma *et al*, 2024; Jabłońska *et al*, 2023). Although *iStent* implantation is successful in controlling IOP and reducing medication dependency, its effect on visual acuity depends on the specific subtype of glaucoma and the pathophysiological mechanisms involved. Clinically, the combination of phacoemulsification and *iStent* may be recommended for patients who require more attention to visual acuity improvement and who also require minimal postoperative anti-glaucoma medication.

However, study design factors and the heterogeneity of the patient population influenced the results, highlighting the importance of personalising interventions based on patient condition and clinician expertise.

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5. Advantages and Limitation

This network meta-analysis study has the advantage of including data from multiple regions (Americas and Europe) with a long follow-up period (1-64 months). The analysis of this study provides clinical recommendations for the management of open-angle glaucoma and integrates the results of previous studies, including Hu *et al.* and Laspas *et al.*, which support the superiority of *Hydrus* over *iStent* in combination with phacoemulsification for significant IOP reduction.

This study extends the approach by using the SUCRA method to determine a more scalable treatment sequence, providing an advantage over previous research analyses. Limitations of this study include the lack of direct comparison for some parameters, such as visual acuity (BCVA ≥ 20/40) and postoperative medication requirements, between the combination of *Hydrus* and *iStent* with phacoemulsification.

Nevertheless, this review broadens the understanding of the safety and efficacy of MIGS, particularly *Hydrus* and *iStent*, and opens up opportunities for further research to address the limitations of existing direct data.

6. Conclusion

The conclusions that can be drawn from this study are

1. There was a greater reduction in intraocular pressure in patients with open-angle glaucoma who received *Hydrus* combined phacoemulsification than *iStent* phacoemulsification or phacoemulsification alone.

2. There was an improvement in visual acuity in open-angle glaucoma patients treated with *iStent* phacoemulsification compared with *Hydrus* phacoemulsification or phacoemulsification alone.

3. There was a reduction in the number of anti-glaucoma medications in open-angle glaucoma patients treated with *iStent* phacoemulsification compared to *Hydrus* phacoemulsification or phacoemulsification alone.

4. There were fewer types of complications in open-angle glaucoma patients who received combined *iStent* and phacoemulsification surgery.

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