


Determining the Superiority of Vitrectomy vs Aflibercept for Treating Dense Diabetic Vitreous Hemorrhage: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract: This review aimed to systematically compare the efficacy and safety of intravitreal aflibercept (IVA) and vitrectomy for treating severe vitreous hemorrhage (VH) secondary to proliferative diabetic retinopathy (PDR). The review was conducted in accordance with PRISMA guidelines. A search strategy, including the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and US National Library of Medicine databases, was developed to identify randomized controlled trials (RCTs) that compared vitrectomy and IVA for managing VH due to PDR (participant age ≥ 18 years). The primary outcome measure was the difference in the mean visual acuity between the two treatment groups at 1, 6, and 24 months. Outcome measures included clearance of VH (in weeks), the incidence of recurrent VH, and the rate of complications. The studies were evaluated using the Cochrane Bias (ROB) tool. We identified 774 articles; six articles met the inclusion criteria, and two were ultimately included ($n = 239$ eyes). With or without PRP, IVA injections and vitrectomy were performed in 117 and 122 eyes, respectively. The mean BCVA at one month was significantly better in the vitrectomy group (MD=0.22, CI:0.10–0.34, $p=0.0003$), but no difference was found at six months (MD=0.04, CI: -0.04–0.12, $p=0.356$). The incidence of recurrent VH was significantly higher in the IVA group (OR=5.05, CI:2.71–9.42, $p<0.0001$). The probability of recurrent VH was five times greater in the IVA group than that in the vitrectomy group. There were no significant differences in the overall proportions of intra- or postoperative complications (OR=0.64, CI: 0.09–4.85, $p=0.669$). None of the studies had a low ROB in any of the seven domains. We conclude that IVA can be considered a viable treatment modality for diabetic VH in patients with a good follow-up. Vitrectomy initially provides better visual effect, faster VH recovery, and lower VH recurrence than IVA injections.

Keywords: aflibercept, anti-VEGF, intravitreal injection, proliferative diabetic retinopathy, vitrectomy

Introduction

Diabetic retinopathy (DR) is the leading cause of permanent visual impairment worldwide.¹ Secondary consequences of DR in the eye include multiple vision-threatening complications such as diabetic macular edema (DME) and vitreous hemorrhage (VH) secondary to proliferative diabetic retinopathy (PDR).² PDR is traditionally treated using panretinal photocoagulation (PRP).³ However, PRP can cause permanent vision loss in the peripheral visual field, reduce contrast sensitivity, and delay adaptation to darkness.^{2,4,5} Surgical treatment options for PDR include pars plana vitrectomy (PPV), which has been practiced since the 1970s. Although there have been improvements in instrumentation and surgical techniques, the frequency of performing vitrectomy has decreased over the years and is usually reserved for the most difficult cases.⁶ Newer treatment methods, such as antiangiogenic agents, are increasing in popularity as they have

been found to be effective in stabilizing vision in PDR.⁷ Bevacizumab, ranibizumab, and aflibercept are the most commonly used intravitreal anti-vascular endothelial growth factors (anti-VEGF).⁷

The management of VH in PDR is difficult because of its recurrence and poor visual outcomes. Although surgical, laser and pharmacological procedures are currently used in clinical practice, no single treatment has been proven to be “1 and done”. Therefore, there is a need to identify new treatment methods that are effective in the long term. Several treatment modalities for diabetic VH have been investigated, including intravitreal aflibercept (IVA) injections. Aflibercept is a humanized recombinant fusion protein that binds to VEGF to exert inhibitory effects on VEGF receptors, thereby preventing endothelial proliferation, vascular permeability, and neovascularization. It binds to VEGF with a greater affinity than bevacizumab or ranibizumab^{8,9} and has been shown to be a promising anti-VEGF agent. In addition, IVA has been shown to be no worse than PRP in the treatment of PDR.¹⁰ Koshchynets et al reported a case demonstrating the efficacy of intravitreal aflibercept in combination with PRP for the regression of neovascularization and prevention of recurrent vitreous hemorrhage in a patient with severe type 1 diabetes having total vitreous hemorrhage.¹¹ In a prospective study, Umanets et al, reported that intravitreal aflibercept resulted in the obliteration of neovascularization of epiretinal membranes (ERMs) and avoided intraoperative and postoperative bleeding during vitrectomy.¹² The procedure resulted in a significant improvement in visual outcomes across all cases. Based on case studies and nonrandomized trials, aflibercept has shown efficacy and safety in the management of vitreous hemorrhage in diabetic eye diseases.

Some studies have compared the efficacy of IVA with that of vitrectomy in diabetic VH; however, most of the information presented in the literature is limited to uncontrolled clinical studies or retrospective case series. The results of such studies are inconclusive because of their high risk of bias. Therefore, it is necessary to assess the safety and efficacy of IVA, which can be achieved through a comprehensive meta-analysis. In this review, we sought to systematically establish the efficacy and safety profiles of IVA and vitrectomy in cases of VH secondary to DR to inform future studies with possible clinical benefits. To this end, this systematic review aimed to identify, appraise, and synthesize evidence on the safety and efficacy of two different treatment modalities for VH secondary to DR.

Methods

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines.¹³ A search strategy [see [Appendix - I](#) in the [Supplementary File](#)] was developed to identify all articles that reported vitrectomy and IVA as treatments for VH secondary to PDR.

Study Eligibility Criteria

Studies were selected for inclusion based on the prespecified Population, Intervention, Comparator, Outcomes (PICO) criteria ([Table 1](#)). Randomized controlled trials (RCTs) that reported the use of either vitrectomy or IVA to treat VH secondary to PDR were eligible for inclusion. Conference abstracts, animal studies, non-RCTs, and case series were excluded.

Table 1 PICO Criteria for the Inclusion of Studies

Parameter	Study Selection Criteria
Population	People with vitreous hemorrhage secondary to diabetic retinopathy, age ≥ 18 years
Intervention	Pars Plana Vitrectomy
Comparator	Intravitreal Aflibercept injections
Outcomes	Primary outcome(s): mean visual acuity difference at 1, 6 and 24 months between IVA and Vitrectomy group. Secondary outcome (s): Duration of vitreous hemorrhage clearance (weeks), incidence of recurrent vitreous hemorrhage (frequency), proportion and types of complications between the two groups.

Abbreviation: PICO, Population Intervention Comparator Outcomes.

Search Strategy

The following electronic bibliographic databases were searched: Medline, Embase, Cochrane Central Register of Controlled Trials, and the US National Library of Medicine. English keywords were used to identify studies in these databases published before November 25, 2022. The bibliographies of the included articles were also searched to identify relevant studies.

Data Extraction and Management

Two reviewers (MAQR and VLG) independently screened the titles and abstracts identified in the bibliographic search. Full-text reviews and data extraction were performed independently, and discrepancies were resolved by comparison with the inclusion criteria. Data were extracted using a standardized proforma and included study design, inclusion criteria, participant demographics (age, sex, and underlying conditions), intervention type, and outcome data. Additionally, the sample size, follow-up duration, time to VH resolution, incidence of recurrent VH, and reported complications were also extracted. The mean logMAR visual acuity at the baseline and follow-up visits was also determined.

Risk of Bias Assessment

The Cochrane Collaboration tool was used to assess the risk of bias (ROB) [see [Appendix II for Supporting Information in the Supplementary File](#)].¹⁴ This tool incorporates several domains that assess sampling methods, randomization, reporting bias, and detection bias. Two reviewers (MAQR and VLG) independently assessed the ROB in each RCT across the seven domains. Disagreements were resolved through consensus.

Measures of Treatment Effect

The primary outcome measure was the mean difference in the best-corrected visual acuity (BCVA) in logMAR units at 1, 6, and 24 months. The secondary outcome measures included the duration of VH clearance after treatment (weeks), recurrence of VH (frequency), and complications. Complications were defined as worsening conditions requiring adjunctive treatment or adverse effects after treatment. Data were reported across studies, with widely varying time points and outcome assessors. Therefore, the other outcome measures reported in the included studies were extracted and interpreted. The meta-analysis was performed using the R statistical package.

Results

The literature search yielded 774 articles, of which 6 were eligible for inclusion. A full-text review identified four articles to be excluded (one uncontrolled study,¹⁵ one study in which IVA was compared to sham treatment,¹⁶ and two studies in which IVA was compared with PRP)^{10,17}, and ultimately, only two articles were included in the qualitative and quantitative synthesis. The PRISMA flowchart for the selection of studies is shown in [Figure 1](#). The first study was conducted across 39 Diabetic Retinopathy Clinical Research (DRCR) Retina Network sites in the United States and Canada.¹⁸ The study recruited 205 participants between November 2016 and December 2017 and conducted final follow-up in January 2020. Another study was conducted at two eye centers, one each in Kuwait and Egypt.¹⁹ The study recruited 34 participants between March 2018 and July 2019.

This meta-analysis included 239 eyes (one eye per participant). Among these, 117 eyes received IVA injections with or without panretinal photocoagulation (PRP) and 122 eyes received vitrectomy with or without PRP. The participants were randomly allocated to receive either IVA with or without PRP, or vitrectomy with or without PRP. Participants in the IVA group received three¹⁹ or four monthly doses of IVA injections¹⁸ (EYLEA; Regeneron Pharmaceutical Inc., Tarrytown, NY, USA) at a dose of 2 mg/0.05 mL. Seventeen participants in the IVA group received PRP in addition to IVA injections. PPV with or without PRP was performed in participants in the other group. The participants were followed up for two years in one study, and for nine months in another study. The characteristics of the included studies are summarized in [Table 2](#).

Meta-Analysis of Best-Corrected Visual Acuity (BCVA) at 1 and 6 Months

The mean BCVA data were available at baseline and at 1, 3, 6, and 9 months from one study,¹⁹ and at baseline, 1 month (4 weeks), 6 months (24 weeks), and 2 years from the other study.¹⁸ The mean BCVA in the IVA group and the vitrectomy group in the two

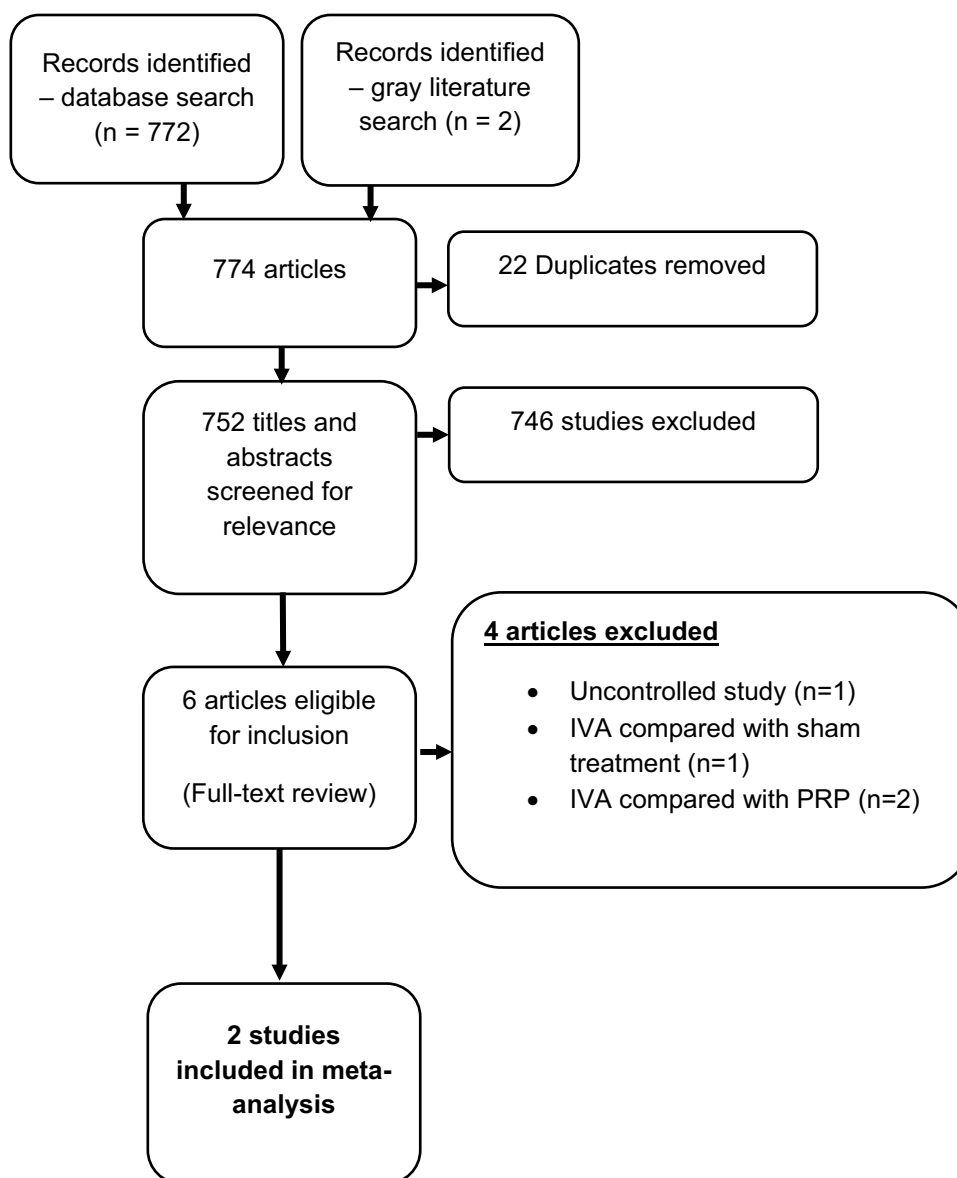


Figure 1 PRISMA flow chart outlining the article selection process.

included studies at the 1-month and 6-month follow-ups were pooled to assess the difference between the two groups. The mean BCVA values at different follow-up times in the two included studies are shown in [Table 3](#). The mean BCVA in the vitrectomy group was significantly better at one month than at six months (MD=0.22, CI: 0.10–0.34, $p=0.0003$). There was no significant difference in BCVA between the two groups (MD=0.04, CI: –0.04–0.12, $p=0.356$). There was no heterogeneity between the groups at either 1 month ($I^2=0.00\%$, $Q(df=1)=0.491$, $p=0.483$) or 6 months ($I^2=0.00\%$, $Q(df=1)=0.477$, $p=0.490$). Forest plots for the mean difference in BCVA at the 1-month and 6-month follow-ups are shown in [Figures 2](#) and [3](#), respectively. Similarly, no significant difference in mean visual acuity between the two groups was observed at 24 months in the Antoszyk et al¹⁸ study.

Duration for Vitreous Hemorrhage Clearance

Abd Elhamid et al¹⁹ reported a mean duration of 7.8 weeks (SD ± 1.8) in the aflibercept group and five days in the vitrectomy group. Similarly, in a secondary analysis of Glassman et al²⁰ study reported the median time for the clearance of VH as 36 weeks (IQR, 24–52 weeks) in the aflibercept group and 4 weeks (IQR, 4–4 weeks) in the vitrectomy group. Both studies reported a significantly faster clearance of VH in the vitrectomy group than in the aflibercept group.

Table 2 Characteristics of the Included Studies

(A). Characteristics of the intravitreal aflibercept (IVA) group												
First author/ Publication year	Study year	Countries	Study design	Outcome measure(s)	Mean age (SD) (years)	Sample size (eyes included)	Mean duration of diabetes (SD) (years)	No. of Aflibercept injections given	Any secondary intervention	Duration of vitreous hemorrhage clearance (weeks)	Duration of follow up (months)	No. of eyes with recurrent vitreous hemorrhage
Abd-Elhamid et al ¹⁹	2019	Kuwait and Egypt	RCT	Primary outcome(s) • Change in mean visual acuity after 9 months Secondary outcome(s) • Mean duration of vitreous hemorrhage clearance • Rate of recurrent vitreous hemorrhage • Complications	56.4 (8.6)	17	16.4 (3.8)	3 (monthly doses 2 mg/0.05 mL)	PRP after last dose of IVA in case of vitreous clearance	7.8 (1.8)	9	5/17
Antoszyk et al ¹⁸	2016	US and Canada	RCT	Primary outcome(s) • Mean visual acuity over 24 weeks Secondary outcome(s) • Mean visual acuity at 4 weeks and 2 years	56 (12)	100	19 (10)	4 (monthly doses of 2 mg/0.05 mL at baseline, 4, 8 and 12 weeks)	NA	36	24	48/97
(B). Characteristics of the vitrectomy group												
First author/ publication year	Study year	Country	Study design	Outcome measure(s)	Mean age (SD) years	Sample size (eyes included)	Duration of diabetes (SD) years	Time for clearance of vitreous hemorrhage (weeks)	Duration of follow up (months)	Any other secondary intervention	No. of eyes with recurrent vitreous hemorrhage	
AbdElhamid AH 2020 ¹⁹	2019	Kuwait and Egypt	RCT	Primary outcome(s) • Change in mean visual acuity after 9 months Secondary outcome(s) • Mean duration of vitreous hemorrhage clearance • Rate of recurrent vitreous hemorrhage • Complications	58.8 (7.9)	17	15.8 (3.9)	5 days	9	NA	2/17	
Antoszyk AN 2020. ¹⁸	2016	US and Canada	RCT	Primary outcome (s) • Mean visual acuity over 24 weeks Secondary outcome (s) • Mean visual acuity at 4 weeks and 2 years	57 (11)	105	21 (11)	4	24	PRP	16/104	

Abbreviations: IVA, intravitreal aflibercept; RCT, randomized controlled trials; SD, standard deviation.

Table 3 Mean BCVA in the Aflibercept and Vitrectomy Groups at Different Follow-Up Visits

Study	Follow-up	Aflibercept		Vitrectomy	
		N	LogMAR BCVA Mean (SD)	n	LogMAR BCVA Mean (SD)
bd Elhamid et al ¹⁹	Baseline	17	1.17 (0.48)	17	1.44 (0.44)
	1-month	17	0.93 (0.37)	17	0.65 (0.22)
	6-months	17	0.52 (0.19)	17	0.46 (0.10)
	9-months	17	0.51 (0.20)	17	0.48 (0.18)
Antoszyk et al ¹⁸	Baseline	100	1.00 (0.53)	105	1.03 (0.54)
	1 months	95	0.63 (0.51)	99	0.44 (0.53)
	6 months	97	0.32 (0.47)	98	0.32 (0.50)
	24 months	90	0.22 (0.40)	87	0.25 (0.47)

Abbreviations: BCVA, best-corrected visual acuity; SD, standard deviation.

Incidence of Recurrent Vitreous Hemorrhage

The incidence of recurrent VH was reported in both included studies. The incidence of recurrent VH was significantly higher in the aflibercept group (odds ratio [OR]=5.05, CI:2.71–9.42, $p<0.0001$). The odds of recurrent VH were five times higher in the aflibercept group than in the vitrectomy group. There was no heterogeneity among the studies when assessing the incidence of recurrent VH ($I^2=0.00\%$, $Q(df=1)=0.31$, $p=0.579$). The pooled incidence of recurrent vitreous hemorrhage is shown in [Figure 4](#).

Complications

Intraoperative or postoperative complications occurred in both the included studies. A summary of the ocular complications in the two studies is presented in [Table 4](#). Cataracts in the phakic eyes were the most commonly reported complications in both groups. Other complications include new or worsened retinal detachment, tears, ERMs, and endophthalmitis. The overall proportion of intra- or postoperative complications was not significantly different between the groups ($OR=0.64$, $CI:0.09–4.85$, $p=0.669$). However, substantial heterogeneity was observed when estimating the pooled proportions of overall ocular complications between groups ($I^2=79.50\%$, $Q(df=1)=4.88$, $p=0.027$). The odds ratios and proportions of ocular complications are shown in [Figure 5](#).

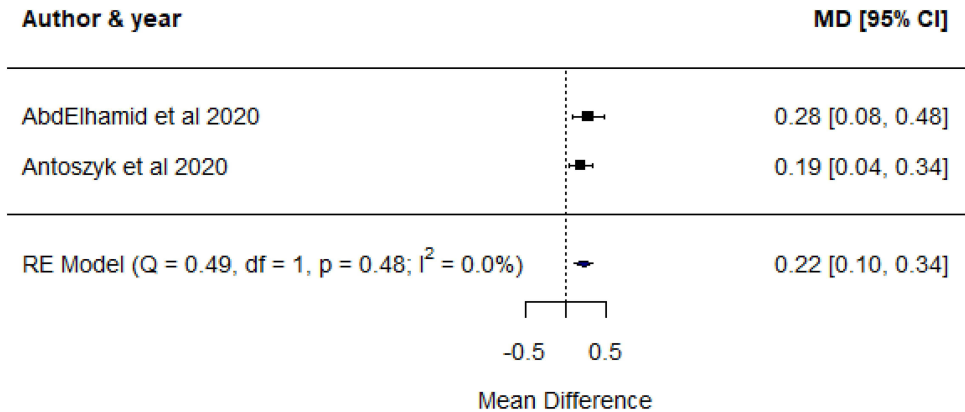


Figure 2 Mean difference in BCVA at 1-month follow-up visits.

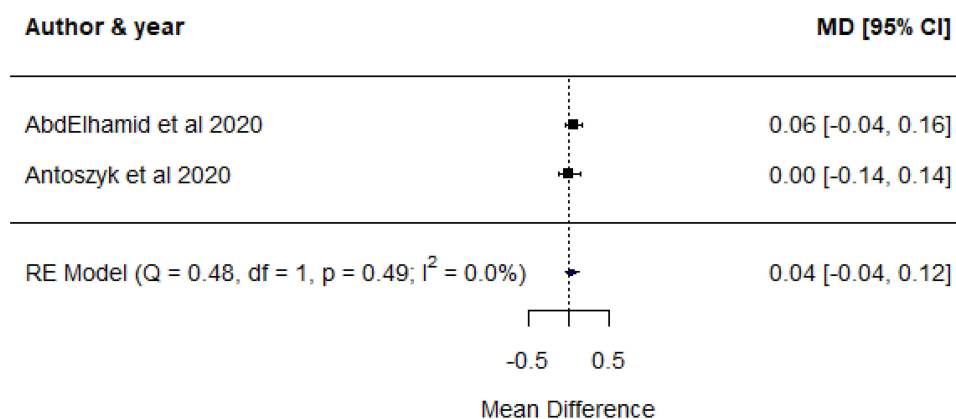


Figure 3 Mean difference BCVA at 6-month follow-up visits.

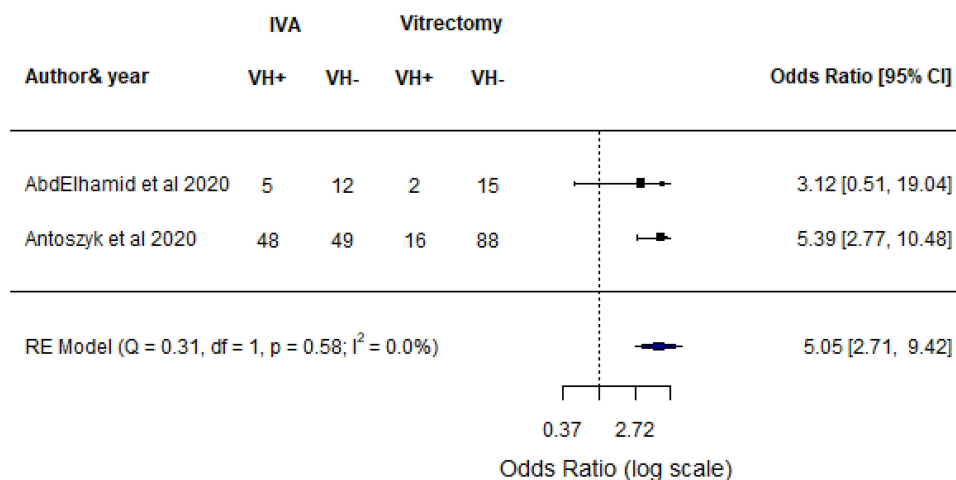


Figure 4 Pooled incidence of recurrent vitreous hemorrhage.

Study Quality

Figure 6 summarizes the ROB assessments of the included studies. None of the studies was judged to have a low ROB in any of the seven domains. Antoszyk et al¹⁸ were judged to have a low risk of bias across most domains (5/7 domains), while Abd Elhamid et al¹⁹ were judged to have a low risk of bias across only two domains.

Table 4 Ocular Complications in the IVA and Vitrectomy Groups

Author/Year	Complications	
	Aflibercept Group	Vitrectomy Group
Abd Elhamid et al ¹⁹	Epiretinal membrane (2/17 eyes)	Cataract (4/11 phakic eyes) Epiretinal membrane (2 eyes) Intraoperative retinal tear (2 eyes), Significant intraoperative bleeding (1 eye)
Antoszyk et al ¹⁸	Cataract (37/75 eyes) Tractional RD (22 eyes) New or worsened rhegmatogenous RD (4 eyes) Endophthalmitis (1 eyes)	Cataract (36/81 eyes) Tractional RD (14 eyes) New or worsened Rhegmatogenous RD (5 eyes) Endophthalmitis (2 eyes)

Abbreviations: IVA, intravitreal aflibercept; RD, retinal detachment.

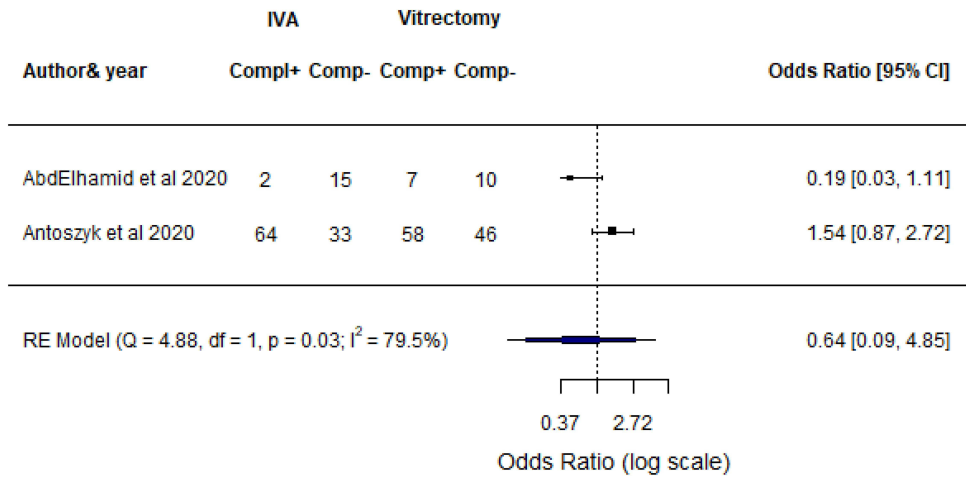


Figure 5 Proportions of ocular complications.

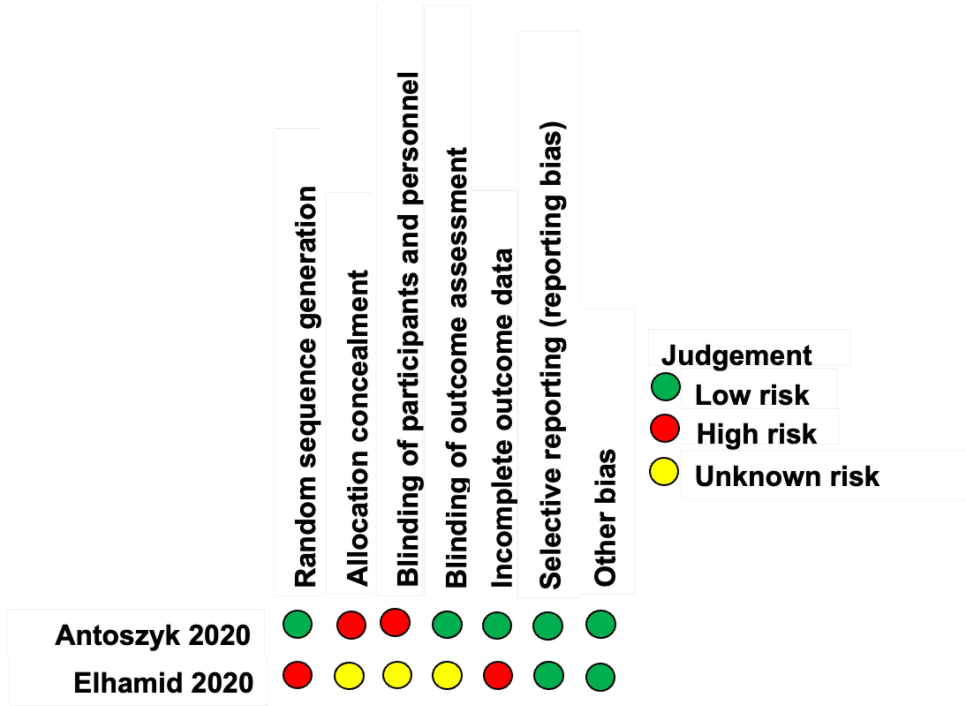


Figure 6 Risk of bias assessment of the included studies.

Discussion

Vitrectomy and PRP have been widely used for the treatment of diabetic VH since the 1970s.⁶ However, the role of anti-VEGF agents, including IVA, has increased over the last few years.²¹ IVA is less invasive than vitrectomy. This makes IVA a good choice for the treatment of diabetic retinopathy.¹⁰ However, the potential benefits and safety of IVA in the treatment of VH are not clearly understood. Therefore, the aim of the present systematic review and meta-analysis was to identify a better functional approach between the two modalities of treatment for diabetic VH, that is, vitrectomy versus IVA.

The primary outcome measure of this review was the mean difference in visual acuity at 1, 6, and 24 months postintervention. Although the visual acuity outcome was better in the vitrectomy group in the early stages, there was no

difference in the long-term recovery between the two interventions. The secondary outcome measures of the review were the duration of VH clearance and occurrence of recurrent VH postintervention. VH clearance was faster in the vitrectomy group than that in the IVA group. Similarly, the odds of recurrent VH were higher in the IVA group than those in the vitrectomy group. Historical observations have highlighted the association between intravitreal treatment and visual outcomes. Retinal thickness deviation, which indicates the deviation of central subfoveal thickness from normative values, has previously been shown to be strongly associated with visual outcomes in patients with diabetic macular edema undergoing intravitreal treatment.²²

Previous studies have confirmed the beneficial effects of IVA in treating diabetic retinal disease, particularly DME. Chen et al²³ reported that three monthly intravitreal aflibercept injections yielded benefits in nearly two-thirds of cases of DME resistant to bevacizumab or ranibizumab over a short-term follow-up. IVA has been observed to be safe and effective in submacular hemorrhage secondary to neovascular AMD,²⁴ in resolving rubeosis iridis secondary to proliferative diabetic retinopathy with VH,²⁵ and in macular edema secondary to central retinal vein occlusion.²⁶ IVA has been tested in multiple retinal diseases; however, specific literature regarding its safety and efficacy in VH due to diabetic retinopathy is lacking. Therefore, in the current literature, only two studies with similar study protocols could be combined to compare the treatment outcomes after IVA and vitrectomy.

However, the safety of the two interventions was inconclusive because of the high heterogeneity in estimating the results.²⁷ The proportions of intra- or postoperative ocular complications were not significantly different between the two groups. Cataracts in the phakic eyes were the most common complications that occurred in both the vitrectomy and IVA groups. The development of cataracts after vitrectomy is a well-known complication.²⁸ Other complications noted in both groups were tractional retinal detachment (TRD), new or worsened rhegmatogenous RD, ERMs and endophthalmitis. Further RCTs on the safety of these two interventions are warranted to clearly understand the differences in complications between the two groups.

The results of this study have several potential clinical implications. Given the insignificant differences in complication rates between the two groups and the relatively lower invasiveness of IVA, it can be considered a good choice in terms of long-term visual outcomes. However, the frequent administration required to overcome recurrent VH, which has a higher incidence after IVA, may not make IVA an ideal choice for patients with poor follow-up. Since the incidence of recurrent VH and the duration of VH clearance were significantly better in the vitrectomy group, it should be considered superior to IVA in terms of these treatment outcomes. Therefore, in patients requiring faster recovery from the hemorrhage, particularly in one-eyed patients with VH in the better eye, vitrectomy can be considered a better treatment choice.

Risk of Bias Assessment

The two studies that examined the safety and efficacy of IVA for VH due to diabetic retinopathy had a high risk of performance bias. This is because surgical interventional studies on cases of profound visual loss secondary to diabetic retinopathy are likely to have inherent variability because of the seriousness of the disease; patient masking and clinician masking are usually difficult, as shared decision making is needed to determine the intervention applied.²⁹ Additionally, patients are likely to decline newer treatment methods when given choice over an existing successful treatment method.³⁰ This review included only RCTs for a stronger assessment, although non-RCTs and case series also provide information on unintended or long-term effects of an intervention.^{29,31}

The strength of our meta-analysis was that we included only RCTs that offered the highest level of evidence. All noncontrolled trials were excluded. However, a major limitation of our review was the insufficient evidence available for its synthesis. Further RCTs are required to confirm the findings of the present study.

Conclusions

The present meta-analysis showed that intravitreal aflibercept can be a viable treatment modality for diabetic VH, given its similar long-term visual outcomes to vitrectomy in patients who maintain long-term follow-up visits. Nevertheless, vitrectomy provides a better initial visual outcome, faster recovery of VH, and lower recurrence of VH than IVA

injections, and therefore shows superior surgical outcomes. However, there was no significant difference in the proportion of complications between the two modalities of treatments. The limited number of RCTs comparing these two interventions suggests the need for additional high-quality studies to confirm these findings.

Abbreviations

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CI, confidence interval; DME, diabetic macular edema; DR, diabetic retinopathy; DRCR, Diabetic Retinopathy Clinical Research; IVA, intravitreal aflibercept; LogMAR, logarithm of the minimum angle of resolution; MD, median deviation; PRP, panretinal photocoagulation; PDR, proliferative diabetic retinopathy; PICO, Population, Intervention, Comparator, Outcomes; OR, odds ratio; PPV, pars plana vitrectomy; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs, randomized controlled trials; RD, retinal detachment; ROB, Risk of Bias; VEGF, vascular endothelial growth factor; TRD, tractional retinal detachment; VH; vitreous hemorrhage.

Summary Statement

The management of vitreous hemorrhage in proliferative diabetic retinopathy is difficult because of its recurrence and poor visual outcomes. This systematic review compared the safety and efficacy of intravitreal aflibercept versus vitrectomy for the treatment of this condition by synthesizing evidence on the safety of the two different treatment modalities.

Data Sharing Statement

The datasets used in this study are included in the main article. Figures from this study may be released via a written application to the Photographic Laboratory and Clinical Archives at Oftalmologia Integral ABC, Medical and Surgical Assistance Institution (Nonprofit Organization), Av. Paseo de las Palmas 735 suite 303, Lomas de Chapultepec, Mexico City 11000, Mexico and the corresponding author upon request.

Ethics Approval and Consent to Participate

This study adhered to the tenets of the Declaration of Helsinki and received full approval from the appropriate research ethics committee, institutional review committee, and institutional teaching department (the institutions did not provide reference numbers for systematic reviews and meta-analyses).

Institutional Review Board Statement

This study was conducted in the Retina Department of the Oftalmologia Integral ABC Institution in Mexico City, Mexico. The Institutional Review Board approved the study's institutional guidelines. No reference numbers were provided for the systematic review and meta-analysis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest.

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