Intravitreal bevacizumab prior to vitrectomy for proliferative diabetic retinopathy: a systematic review

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Abstract

Background: Diabetic retinopathy is a leading cause of visual loss in the working population. Pars plana vitrectomy has become the mainstream treatment option for severe proliferative diabetic retinopathy (PDR) associated with significant vitreous haemorrhage and/or tractional retinal detachment. Despite the advances in surgical equipment, diabetic vitrectomy remains a challenging operation, requiring advanced microsurgical skills, especially in the presence of tractional retinal detachment. Preoperative intravitreal bevacizumab has been widely employed as an adjuvant to ease surgical difficulty and improve postoperative prognosis. **Aims:** This study aims to assess the effectiveness of preoperative intravitreal bevacizumab in reducing intraoperative complications and improving postoperative outcomes in patients undergoing vitrectomy for the complications of PDR.

Methods: A literature search was conducted using the PubMed, Cochrane, and ClinicalTrials. gov databases to identify all related studies published before 31/10/2020. Prespecified outcome measures were operation time, intraoperative iatrogenic retinal breaks, bestcorrected visual acuity in the last follow-up visit, the presence of any postoperative vitreous haemorrhage and the need to re-operate. Evidence synthesis was performed using Fixed or Random Effects models, depending on the heterogeneity of the included studies. Heterogeneity was assessed using Q-statistic and I². Additional meta-regression models, subgroup analyses and sensitivity analyses were performed as appropriate.

Results: Thirteen randomized control trials, with a total of 688 eyes were included in this review. Comparison of the intraoperative data showed that bevacizumab reduced operation time (p < 0.001), minimized iatrogenic retinal breaks (p < 0.001), provided better long-term visual acuity outcomes (p = 0.005), and prevented vitreous haemorrhage (p < 0.001) and the need for reoperation (p = 0.001 < 0.05). Findings were strongly corroborated by additional sensitivity and subgroup analyses.

Conclusion: Preoperative administration of bevacizumab is effective in reducing intraoperative complications and improving the postoperative prognosis of diabetic vitrectomy.

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Keywords: bevacizumab, diabetic retinopathy, systematic review, vitrectomy

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Introduction

Diabetic retinopathy (DR) is one of the leading causes of legal blindness in working-age adults.^{1–3}

It consists of two different clinical entities, nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The Meta-analysis

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Diabetic Retinopathy Study proved the efficacy of retinal photocoagulation in the treatment of established PDR.⁴

Proliferative diabetic retinopathy is defined by the presence of neovascularization, either within 1 diameter of the optic disc (NVD) or elsewhere (NVE) in the retina. Connective tissue forms around these new vessels and into the vitreous, causing vitreous traction to be transmitted to both the new vessels themselves and adjacent retina. These can induce vitreous haemorrhage (VH) and tractional retinal detachment (TRD)⁵ which can be vision-threatening, if not treated appropriately.^{6,7} Pars plana vitrectomy (PPV) plays pivotal role in the management of PDR complications. Non clearing VH, diabetic macular oedema mainly due to macular traction, macular involving or macular threatening TRD and combined tractional-rhegmatogenous RD are the main indications.^{8,9} Surgery aims to remove blood and vitreous from the vitreous cavity, relieving retinal traction and allowing laser endophotocoagulation. Despite the challenging nature of this surgery, recent advances in surgical equipment with the introduction of minimally invasive vitrectomy techniques using small gauge instruments, high-speed cutters and the ability to perform intraoperative laser endophotocoagulation lowered the threshold for surgical treatment, reduced complications and improved outcomes.^{10,11} However, a variety of intra- and postoperative complications are still described.9 These include iatrogenic retinal breaks, prolonged operation time, intraoperative bleeding, postoperative VH, rubeotic glaucoma and RD.¹²⁻¹⁵ In at least 10% of patients, reoperation is required due to rhegmatogenous RD, recurrent traction, and VH.16 All the above can affect the final visual function and quality of life in these patients.

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Off-label, bevacizumab 1.25 mg/0.05 mL is used intravitreally to halt the progression of PDR.¹⁷ Despite its proven efficacy in inhibiting neovascularization, intravitreal bevacizumab (IVB) in patients with PDR is thought to induce fibrovascular contraction, leading to TRD or aggravating preexisting RD.^{17–19} This is mediated by a reported profibrotic switch following the first few days after IVB administration, with a significant reduction in the neovascular component, but accompanied by a marked increase in the contractile elements (smooth muscle actin and collagen).²⁰

The risk-benefit of preoperative IVB for vitrectomy in severe PDR has been debated.^{20,21} In a few observational studies, preoperative IVB has been reported to reduce surgical time and intraoperative bleeding, hasten anatomic resolution, provide better long-term visual acuity, and reduce the rate of reoperation.²²⁻²⁸ Despite its widespread use, there is lack of a consensus regarding the effect of preoperative IVB on intraoperative complications during PPV, and on postoperative outcomes. Previous systematic reviews have evaluated its efficacy.²⁹⁻³¹ However, since then, several new trials have been published allowing improved meta-analysis of results, particularly for IVB the commonest anti VEGF agent used for this indication globally. The present study attempts to evaluate the use of preoperative IVB in patients undergoing vitrectomy for severe PDR, in terms of intraoperative and postoperative complications, by reviewing all the current literature.

Methods

Evidence acquisition

This study has been conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and is being reported in compliance with the PRISMA Statement guide-lines.^{32,33} The review protocol was submitted and published on Prospero (Registration number: CRD42021219280).

Eligibility criteria

Inclusion criteria. Studies included in the quantitative analysis were compliant with the following criteria:

- Publication date was between 1/1/2006 and 31/10/2020
- They were designed as randomized control trials (RCT)
- The population under study was patients scheduled for vitrectomy for severe PDR
- At least one group in each RCT was randomized to receive IVB no more than 1 month before surgery. Control group was randomized to sham injection or no treatment.

Exclusion criteria. The following exclusion criteria were applied to our study:

- Studies without quantitative reporting of outcomes
- Reports not published in English
- Conference abstracts
- Pilot trials
- Retracted papers
- The use of other anti VEGF agents

Search method

A literature search was conducted using the PubMed, Cochrane and ClinicalTrials.gov databases in order to identify all related studies. Furthermore, for studies retrieved, a manual search of their references was performed to find possible relevant reports. Search criteria included the terms 'Diabetic Retinopathy [MeSH Terms]', 'Bevacizumab [MeSH Terms]' and 'Vitrectomy [MeSH Terms]'.

All titles and abstracts retrieved, were reviewed for eligibility by two independent authors (P.D., N.D.). In case of disagreement, a third author (P.V.) was consulted to reach consensus. For titles and abstracts of possibly eligible studies, full texts were screened by two independent review authors (P.D., N.D.).

Quality assessment

Risk of Bias (RoB) Cochrane Tool for Systematic Reviews of Interventions was used to evaluate the retrieved RCTs.³⁴ RoB assesses several domains of bias, with respect to trial design, conduct and reporting, into low risk, high risk or unclear risk of bias.

Data extraction

Relevant data were extracted into an electronic database. If data were missing, the corresponding authors for published articles were contacted directly to request the data. The following data were retrieved from the included studies: author's name, number of subjects enrolled, indication for vitrectomy, intervention groups and outcomes measured. Two independent authors (P.D., N.D.) carried out RoB assessment and data extraction. In case of disagreement, a third author (P.V.) acted as an arbitrator.

Outcome measures

Primary outcome measures were operation time and iatrogenic intraoperative retinal break occurrence. Secondary outcomes were logMAR best corrected visual acuity (BCVA) on last follow-up visit, occurrence of postoperative vitreous cavity haemorrhage (POVCH) at any time post-operatively and the need for second vitrectomy regardless of cause.

Statistical analysis

Review Manager (Review Manager (RevMan) [Computer programme]. Version 5.4, The Cochrane Collaboration, 2020) was used for all statistical analyses. For continuous data, mean differences (MDs) and 95% confidence intervals (95% CIs) were calculated for each time frame. For binary outcomes, odds ratios (ORs) and 95% CIs were used. Fixed effects (FE) or random effects (RE) were employed for data synthesis. Each study's weight was determined as the inverse variance of individual effects. Heterogeneity among studies was tested with both the Q-statistic and I235 and assumed if $P_0 < 0.1$ or $I^2 > 50\%$. In case of heterogeneity, results were subject to the RE model and heterogeneity was further explored with meta-regression, sensitivity analyses and subgroup analyses. Otherwise, a FE model was applied. Publication bias was assessed with forest plots. In all comparisons, sensitivity analyses were performed with the method of 'leave-one-out'.

Results

Study selection

The study selection flow chart is presented in Table 1. The last literature search was performed on November 1, 2020. Of the 154 potentially relevant studies retrieved from electronic search and related references, 20 were ruled out for duplicity. The remaining 134 records were scanned for eligibility. Finally, 16 met all the predefined inclusion criteria.^{22,36–50} Of these, 3 studies were excluded from the analysis because results could not be pooled in any of the pre-specified comparisons^{22,49,50} leaving 13 studies for inclusion in the meta-analysis.

Studies description and quality assessment

Five studies compared preoperative IVB versus sham injection, ^{36,38,39,44,47} and 8 studies compared

Table 1. Retrieved studies selection flow-chart.



RCT, randomized control trials.

preoperative IVB versus no treatment.^{37,40–43,45,46,48} All but one of the studies included patients suffering not only from non-clearing VH but also from TRD, the exception being the study of Faisal et al. with patients suffering exclusively from VH.⁴¹ In another study, there were two different time frames for preoperative IVB administration.³⁹ These two groups were combined in the present study in order to avoid double counting bias.⁵¹ Moreover, in two other studies IVB concentration used was different than the standard 1.25/0.05 mL.^{44,45} Details on number of cases, indication for vitrectomy, intervention groups and measured outcomes are presented in Table 2.

Studies quality with the RoB Cochrane tool for Systematic Reviews of interventions is presented in Figure 1.

Operation time. Eight studies with a total of 540 patients provided data for the comparison of total operation time. The overall pooled difference among groups after outcome synthesis revealed

decreased total operation time with IVB (RE MD = -20.22 minutes, 95% CI = (-26.25, -14.19), $P_0 = 0.004$, $I^2 = 66\%$ (Figure 2)).

Included studies showed significant heterogeneity, requiring RE model analysis. Subgroup analysis was used for heterogeneity exploration. Studies including patients who received IVB less than 5 days preoperatively and 5 to 21 days preoperatively were analysed separately. Five days was used as a limit because of VH resorption and significant regression of neovascularization being reported the first few days after IVB administration.^{36,40,46} Benefits of preoperative IVB remained statistically significant in all comparisons (Figures 3 and 4), although the studies administering IVB more than 5 days preoperatively were found to reduce operation time slightly more. More specifically, in the less than 5 days subgroup, IVB reduced operation time by 17.90 minutes (RE MD = -17.90 minutes, 95% CI = (-30.14, -5.67), $P_0 = 0.06$, $I^2 = 60\%$ (Figure 3)), while in the 5–21 days subgroup IVB reduced operation time by

STUDY	CASES	INDICATION FOR VITRECTOMY	IN	TERVENTION GROUPS	οι	JTCOMES MEASURED
Ahmadieh 2009	68	Non-clearing VH, TRD, active or progressive PDR	•	IVB 1.25 mg – 1 week pre-op Sham – 1 week pre-op	•	Post-op VH BCVA Adverse events
Ahn 2011	107	Non-clearing VH, TRD, vitreoretinal adhesions	•	IVB 1.25 mg – 1–14 days pre-op IVB 1.25 mg – intra-op No IVB	•	Post-op VH BCVA Initial time of vitreous clearing
Arevalo 2019	214	TRD with or without RRD, with or without VH	•	IVB 1.25 mg – 3-5 days pre-op Sham – 3-5 days pre-op	• • • •	Intraoperative bleeding Iatrogenic retinal break Post-op VH BCVA improvement Central Retinal Thickness Retinal Redetachment Adverse events
Di Lauro 2010	72	VH, TRD	•	IVB 1.25 mg – 1 week pre-op IVB 1.25 mg – 3 weeks pre-op Sham – 3 weeks pre-op	• • • •	Intraoperative bleeding Endodiathermy Iatrogenic retinal break Relaxing Retinotomy Operation Time Post-op VH
El-Batarny 2008	30	VH, TRD	•	IVB 1.25 mg – 5-7 days pre-op No IVB	• • • • •	Operation time Intraoperative bleeding Endodiathermy Iatrogenic retinal break Retinotomies Tamponade RD BCVA Post-op VH Adverse events
Faisal 2018	56	VH	•	IVB 1.25 mg – 7 days pre-op No IVB	•	Surgical time latrogenic retinal break Intraoperative bleeding
Farahvash 2011	35	VH, TRD	•	IVB 1.25 mg – 1 week pre-op No IVB	• • • •	IVB adverse events Retinotomies Tamponade Endodiathermy Iatrogenic retinal breaks Score of bleeding RD
Hernandez-Da Mota 2010	40	Advanced PDR, TRD	•	IVB 1.25 mg – 2 days pre-op No IVB	•	Opeartion time Intraoperative bleeding Ocular Hypertension RD Neovascular glaucoma (NVG) Post-op VH Retinotomies

Table 2. Included studies characteristics

(Continued)

Table 2. (Continued)

STUDY	CASES	INDICATION FOR VITRECTOMY	IN	TERVENTION GROUPS	01	JTCOMES MEASURED
Manabe 2015	66	Non-clearing VH, TRD	•	IVB 0.16 mg – 1 day pre-op Sham – 1 day pre-op	• • • • • •	VEGF in vitreous Endodiathermy latrogenic retinal breaks Endotamponade Operational time Post-op VH Elevation of IOP NVG BCVA Second Vitrectomy Adverse events
Modarres 2009	40	TRD	•	IVB 2.5 mg – 3-5 days pre-op No IVB	• • • •	BCVA Endodiathermy Endotamponade Operation time Post-op VH RD Second Vitrectomy
Rizzo 2008	22	TRD, TRD with VH, combined tractional and rhegmatogenous RD	•	IVB 1.25 mg – 5-7 days pre-op No IVB	• • br •	Operation time Intraoperative bleeding Endodiathermy Intraoperative retinal reaks Post-op anatomic tachment
Sohn 2012	20	TRD, combined tractional and rhegmatogenous RD	•	IVB 1.25 mg – 3-7 days pre-op Sham – 3-7 days pre-op	• • •	Vitreous VEGF Vitreous CTGF Intraoperative bleeding Post-op BCVA Endotamponade
Zaman 2013	54	Non-clearing VH, TRD, pre-macular subhyaloid bleeding	•	IVB 1.25 mg – 1 week No IVB	•	BCVA Post-op VH Rubeosis iridis Hyphaema

BCVA, best corrected visual acuity; CTGF, connective tissue growth factor; IOP, intraocular pressure; IVB, intravitreal bevacizumab; PDR, proliferative diabetic retinopathy; RRD, rhegmatogenous retinal detachment; TRD, tractional retinal detachment; VEGF, vascular endothelial growth factor; VH, vitreous haemorrhage.

22.09 minutes (RE MD = -22.09 minutes, 95% CI = (-28.96, -15.22), $P_Q = 0.02$, $I^2 = 71\%$ (Figure 4)). The overlap of the confidence intervals suggests that this difference was not statistically different (Figure 5).

Meta-regression models exploring the number of surgeons performing the operations (p = 0.30), the performance of delamination during surgery (p = 0.42), the performance of combined phaco-vitrectomy versus vitrectomy alone (p = 0.26),

and the mean age of patients (p = 0.57) showed no statistically significant differences for these factors.

Thus, it can be assumed that heterogeneity is due to the different surgeons' experience and skills among studies, surgical equipment, case complexity, and surgical time measuring method. However, operations being performed by the same pre-specified surgeons in each study separately adds to result validation, by decreasing



Figure 1. Risk of Bias assessment of included studies.

	Pr	e-op IVI	3		lo IVB			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Arevalo 2019	71.3	32.1	102	83.6	38.7	112	14.0%	-12.30 [-21.80, -2.80]	
di Lauro 2010	67	19.45	48	84	12	24	16.4%	-17.00 [-24.30, -9.70]	
El-Batarny 2008	61.6	14.5	15	93.3	11.6	15	14.1%	-31.70 [-41.10, -22.30]	—
Faisal 2018	64.1	10.35	28	80.5	10.22	28	18.4%	-16.40 [-21.79, -11.01]	
Hernandez-Da Mota 2010	62	31	20	98	35	20	6.2%	-36.00 [-56.49, -15.51]	
Manabe 2015	49	20	32	56	27	34	12.2%	-7.00 [-18.42, 4.42]	
Modarres 2009	62	57.3	22	95.5	36	18	3.6%	-33.50 [-62.65, -4.35]	
Rizzo 2008	57	9	11	83	11	11	15.2%	-26.00 [-34.40, -17.60]	
Total (95% CI)			278			262	100.0%	-20.22 [-26.25, -14.19]	◆
Heterogeneity: Tau ² = 43.94 Test for overall effect: Z = 6.	l; Chi² = 57 (P < 0	20.61, c).00001	lf = 7 (F)	' = 0.004	4); I² = 6	6%			-50 -25 0 25 50 Favours (pre-op IVB) Favours (No IVB)

Figure 2. Overall estimate of preoperative IVB effect on operation time.

heterogeneity in each study's results and increasing its internal validity.

latrogenic intraoperative retinal break. In order to compare the occurrence of iatrogenic intraoperative retinal breaks, data from 6 studies, including 498 individuals, were synthesized. Preoperative administration of IVB was associated with significantly less breaks (FE OR = 0.37, 95% CI = (0.24, 0.58), P_O = 0.22, I² = 29% (Figure 6)).

BCVA at the last follow-up visit. For comparing log-MAR BCVA prognosis among groups receiving preoperative IVB or not, data from 6 studies including 440 subjects were synthesized. A statistically, significantly better long-term BCVA was found in the groups treated with preoperative IVB (FE MD = -0.13 logMAR, 95% CI = (-0.22, -0.04), $P_0 = 0.37$, $I^2 = 7\%$ (Figure 7)).

In order to examine whether the analysis of different time frames postoperatively and the inclusion of patients with different baseline logMAR BCVA introduced any heterogeneity, a meta-regression model was applied. Neither the time of last followup visit (p = 0.55) nor baseline logMAR BCVA











Figure 5. Comparison of confidence intervals regarding operation time among primary analysis and subgroup analyses.



Figure 6. Overall estimate of preoperative IVB effect on iatrogenic intraoperative retinal breaks occurrence.

	Pre	op IV	В	N	o IVB			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
Arevalo 2019	0.6	0.48	102	0.7	0.31	112	64.6%	-0.10 [-0.21, 0.01]	
di Lauro 2010	0.84	1.09	48	1.2	1.4	24	1.9%	-0.36 [-1.00, 0.28]	
El-Batarny 2008	0.75	0.68	15	0.91	0.67	15	3.3%	-0.16 [-0.64, 0.32]	
Manabe 2015	0.46	0.54	32	0.43	0.48	34	12.7%	0.03 [-0.22, 0.28]	_
Modarres 2009	1.1	0.4	22	1.4	0.3	18	16.4%	-0.30 [-0.52, -0.08]	_
Sohn 2012	1.04	0.82	9	1.49	0.93	9	1.2%	-0.45 [-1.26, 0.36]	•
Total (95% CI)			228			212	100.0%	-0.13 [-0.22, -0.04]	•
Heterogeneity: Chi ² =	5.36, df	= 5 (P	= 0.37); I ² = 79	6				
Test for overall effect:	Z = 2.84	4 (P = 0	0.005)						Favours [Pre-op IVB] Favours [No IVB]

Figure 7. Overall estimate of preoperative IVB effect on best-corrected visual acuity at the last follow-up visit

	Pre	-op IVI	В	N	lo IVB			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Arevalo 2019	0.6	0.48	102	0.7	0.31	112	66.8%	-0.10 [-0.21, 0.01]	
di Lauro 2010	0.84	1.09	48	1.2	1.4	24	2.0%	-0.36 [-1.00, 0.28]	
El-Batarny 2008	0.75	0.68	15	0.91	0.67	15	0.0%	-0.16 [-0.64, 0.32]	
Manabe 2015	0.46	0.54	32	0.43	0.48	34	13.1%	0.03 [-0.22, 0.28]	
Modarres 2009	1.1	0.4	22	1.4	0.3	18	17.0%	-0.30 [-0.52, -0.08]	-
Sohn 2012	1.04	0.82	9	1.49	0.93	9	1.2%	-0.45 [-1.26, 0.36]	•
Total (95% CI)			213			197	100.0%	-0.13 [-0.22, -0.04]	•
Heterogeneity: Chi ² =	5.34, df	= 4 (P	= 0.25)); I ^z = 25	i%				
Test for overall effect:	Z= 2.77	' (P = 0	0.006)						Favours (Pre-op IVB) Favours (No IVB)

Figure 8. Sensitivity analysis of the effect of preoperative IVB on best corrected visual acuity for patients undergoing vitrectomy alone.

(p = 0.26) were statistically significant. When controlling for combined phacovitrectomy as a confounder, a sensitivity analysis by excluding the only study (El-Batarny)⁴⁰ that reported the performance of combined surgery showed very similar results(FE MD = -0.13, 95% CI = (-0.22, -0.04), P_O = 0.25, I² = 25% (Figure 8)).

POVCH. Data from 9 studies examining 654 patients were synthesized for this comparison. Preoperative IVB administration was associated

with statistically significantly less POVCH (RE OR = 0.21, 95% CI = (0.11, 0.40), $P_Q = 0.03$, $I^2 = 53\%$ (Figure 9)).

Meta-regression models analysing total follow-up time (p = 0.26) and patients' mean age (p = 0.35) were not statistically significant. The fact that follow-up time did not affect the presence of POVCH, suggested that preoperative IVB reduced the incidence of both early and late POVCH.

	Pre-op	IVB	No IV	в		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ahmadieh 2009	9	35	26	33	14.3%	0.09 [0.03, 0.29]	.
Ahn 2011	13	36	18	34	16.1%	0.50 [0.19, 1.31]	
Arevalo 2019	29	102	48	112	20.6%	0.53 [0.30, 0.94]	
di Lauro 2010	3	48	6	24	10.9%	0.20 (0.05, 0.89)	
El-Batarny 2008	0	15	4	15	4.0%	0.08 [0.00, 1.69]	
Hernandez-Da Mota 2010	4	20	8	20	11.5%	0.38 [0.09, 1.54]	
Manabe 2015	1	32	8	34	6.9%	0.10 [0.01, 0.89]	
Modarres 2009	0	22	7	18	4.2%	0.03 (0.00, 0.65)	·
Zaman 2013	3	24	20	30	11.4%	0.07 [0.02, 0.30]	
Total (95% CI)		334		320	100.0%	0.21 [0.11, 0.40]	◆
Total events	62		145				
Heterogeneity: Tau ² = 0.47; 0	Chi ² = 17.	20, df=	8 (P = 0.	03); l² =	= 53%		
Test for overall effect: Z = 4.6	63 (P < 0.0	00001)	-				Favours [Pre-op IVB] Favours [No IVB]

Figure 9. Overall estimate of preoperative IVB effect on postoperative vitreous cavity haemorrhage.

Study of Subgroup	Pre-op	IVB Total	No IV	/B Total	Moight	Odds Ratio	Odds Ratio
Study of Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ahmadieh 2009	9	35	26	33	34.0%	0.09 [0.03, 0.29]	_
Ahn 2011	13	36	18	34	38.0%	0.50 [0.19, 1.31]	
Arevalo 2019	29	102	48	112	0.0%	0.53 [0.30, 0.94]	
di Lauro 2010	3	48	6	24	0.0%	0.20 [0.05, 0.89]	
El-Batarny 2008	0	15	4	15	0.0%	0.08 [0.00, 1.69]	
Hernandez-Da Mota 2010	4	20	8	20	28.0%	0.38 [0.09, 1.54]	
Manabe 2015	1	32	8	34	0.0%	0.10 [0.01, 0.89]	
Modarres 2009	0	22	7	18	0.0%	0.03 [0.00, 0.65]	
Zaman 2013	3	24	20	30	0.0%	0.07 [0.02, 0.30]	
Total (95% CI)		91		87	100.0%	0.26 [0.09, 0.77]	-
Total events	26		52				
Heterogeneity: Tau ² = 0.56;	Chi² = 5.2	5, df = 3	2 (P = 0.0	(7); I ² =	62%		
Test for overall effect: Z = 2.4	44 (P = 0.0	D1)					U.UU5 U.1 1 10 200
							Favours (Pre-op IVB) Favours (No IVB)

Figure 10. Sensitivity analysis of the effect of preoperative IVB on postoperative vitreous cavity haemorrhage for patients undergoing vitrectomy without silicone oil tamponade.

In order to examine for the confounding effect of silicone oil tamponade on the occurrence of POVCH in patients pretreated with IVB, a sensitivity analysis was performed by excluding the studies of Arevalo et al., Di Lauro et al., El Batarny et al., Manabe et al., Modarres et al., and Zaman et al. all of which included patients treated with silicone oil. This analysis provided similar results (RE OR = 0.26, 95% CI = (0.09, 0.77), $P_O = 0.07$, $I^2 = 62\%$ (Figure 10)).

Requirement for revision vitrectomy. The need for revision vitrectomy was analysed by combining data from 8 studies including 589 subjects. Preoperative IVB was associated with a lower risk of revision vitrectomy for any cause (FE OR = 0.32, 95% CI = (0.18, 0.57), P_O = 0.88, I² = 0% (Figure 11)).

In order to increase validity, subgroup analyses examined separately the need for revision vitrectomy by cause. Preoperative IVB was beneficial in preventing revision vitrectomy due to both RD (FE OR = 0.41, 95% CI = (0.19, 0.87), $P_Q = 0.94$, $I^2 = 0\%$) and POVCH (FE OR = 0.36, 95% CI = (0.16, 0.85), $P_Q = 0.46$, $I^2 = 0\%$) (Figures 12 and 13).

Regarding the effect of preoperative administration of intravitreal IVB on recurrent retinal traction, data from 4 studies including 272 patients were combined. Patients who received IVB preoperatively benefitted from statistically significant less chances to develop recurrent retinal traction postoperatively (FE OR = 0.42, 95% CI = (0.18, 0.98), PQ = 0.88, I2 = 0% (Figure 14)).

Sensitivity analyses

For every comparison, additional sensitivity analyses were performed according to the leave-one-out method. All of the comparisons were in accordance with our initial findings (Figures 15–19).

	Pre-op	IVB	No IV	/B		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Ahn 2011	3	36	3	34	6.1%	0.94 [0.18, 5.01]	
Arevalo 2019	9	102	28	112	52.4%	0.29 [0.13, 0.65]	— — —
di Lauro 2010	1	48	2	24	5.6%	0.23 [0.02, 2.72]	
El-Batarny 2008	1	15	2	15	4.0%	0.46 [0.04, 5.75]	
Farahvash 2011	1	18	1	17	2.1%	0.94 [0.05, 16.35]	
Hernandez-Da Mota 2010	1	20	4	20	8.2%	0.21 [0.02, 2.08]	
Manabe 2015	1	32	7	34	14.2%	0.12 [0.01, 1.08]	
Modarres 2009	1	22	1	18	2.3%	0.81 [0.05, 13.92]	
Rizzo 2008	0	11	2	11	5.2%	0.17 [0.01, 3.88]	•
Total (95% CI)		304		285	100.0%	0.32 [0.18, 0.57]	◆
Total events	18		50				
Heterogeneity: Chi ² = 3.78, c	f = 8 (P =	0.88);	I²=0%				
Test for overall effect: Z = 3.9	94 (P < 0.)	0001)					Favours (Pre-op IVB) Favours (No IVB)

Figure 11. Overall estimate of preoperative IVB effect on requirement for revision vitrectomy.

	Pre-op	IVB	No IV	В		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Arevalo 2019	6	102	14	112	55.5%	0.44 [0.16, 1.19]	
El-Batarny 2008	1	15	2	15	8.2%	0.46 [0.04, 5.75]	
Farahvash 2011	1	18	1	17	4.3%	0.94 [0.05, 16.35]	
Hernandez-Da Mota 2010	1	20	4	20	16.8%	0.21 [0.02, 2.08]	
Modarres 2009	1	22	1	18	4.6%	0.81 [0.05, 13.92]	
Rizzo 2008	0	11	2	11	10.6%	0.17 [0.01, 3.88]	• • •
Total (95% CI)		188		193	100.0 %	0.41 [0.19, 0.87]	•
Total events	10		24				
Heterogeneity: Chi ² = 1.21, o	if = 5 (P =	0.94);	I²=0%				
Test for overall effect: Z = 2.3	81 (P = 0.)	02)					Favours [experimental] Favours [control]

Figure 12. Overall estimate of preoperative IVB effect on requirement for revision vitrectomy due to retinal detachment.

	Pre-op	IVB	No IV	/B		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
Ahn 2011	3	36	3	34	14.6%	0.94 [0.18, 5.01]		
Arevalo 2019	3	102	14	112	67.0%	0.21 [0.06, 0.76]		
di Lauro 2010	1	48	2	24	13.5%	0.23 [0.02, 2.72]		
Manabe 2015	1	32	1	34	4.9%	1.06 [0.06, 17.77]		
Total (95% CI)		218		204	100.0%	0.36 [0.16, 0.85]	-	
Total events	8		20					
Heterogeneity: Chi ² =	2.60, df =	3 (P =	0.46); I ² =	:0%				400
Test for overall effect:	Z= 2.34 ((P = 0.0	2)				Favours [Pre-op IVB] Favours [No IVB]	100

Figure 13. Overall estimate of preoperative IVB effect on requirement for revision vitrectomy due to postoperative vitreous cavity haemorrhage.

	Pre-op	IVB	No IV	/B		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Arevalo 2019	6	102	14	112	70.5%	0.44 [0.16, 1.19]	
El-Batarny 2008	1	12	2	10	11.2%	0.36 [0.03, 4.74]	
Farahvash 2011	1	7	1	7	4.8%	1.00 [0.05, 19.96]	
Rizzo 2008	0	11	2	11	13.4%	0.17 [0.01, 3.88]	• • •
Total (95% CI)		132		140	100.0%	0.42 [0.18, 0.98]	-
Total events	8		19				
Heterogeneity: Chi ² =	0.68, df=	3 (P =	0.88); I ^z =	:0%			
Test for overall effect:	Z = 2.02 ((P = 0.0	4)				Favours [Pre-op IVB] Favours [No IVB]

Figure 14. Overall estimate of preoperative IVB effect on recurrent retinal traction.

Study or Subaroup	Mean	SD 10-5	Total	Mean	No IVB	Total	Weight	Mean Difference	Mean Difference
Arevalo 2019	71.3	32.1	102	83.6	38.7	112	0.0%	-12.30 [-21.80, -2.80]	
di Lauro 2010 El-Batarny 2008	67 61.6	19.45 14.5	48 15	84 93.3	12 11.6	24 15	18.9% 16.5%	-17.00 [-24.30, -9.70] -31.70 [-41.10, -22.30]	
Faisal 2018	64.1	10.35	28	80.5	10.22	28	21.1%	-16.40 [-21.79, -11.01]	
Hernandez-Da Mota 2010 Manabe 2015	62 49	31 20	20 32	98 56	35 27	20 34	7.4%	-36.00 [-56.49, -15.51] -7.00 [-18.42, 4.42]	
Modarres 2009	62	57.3	22	95.5	36	18	4.3%	-33.50 [-62.65, -4.35]	
RIZZO 2008	57	9	11	83	11	11	17.0%	-26.00 [-34.40, -17.60]	
Total (95% CI) Heterogeneity Tau ² = 47 25	Chi ² = 1	18.42 dt	176 = 6 (P	= 0.004	5): I ² = 6	150 7%	100.0%	-21.57 [-28.23, -14.90]	◆ ·
Test for overall effect: Z = 6.3	34 (P < 0	.00001)	- 0 (i	- 0.000	/// - 0				-50 -25 0 25 50 Favours (pre-op IVB) Favours (No IVB)
	Pre	e-op IVB			lo IVB			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
di Lauro 2010	67	32.1 19.45	48	83.6	38.7	24	0.0%	-12.30 [-21.80, -2.80] -17.00 [-24.30, -9.70]	
El-Batarny 2008	61.6	14.5	15	93.3	11.6	15	16.8%	-31.70 [-41.10, -22.30]	
Hernandez-Da Mota 2010	62	31	20	98	35	20	8.2%	-36.00 [-56.49, -15.51]	
Manabe 2015 Moderres 2009	49	20	32	56 95 5	27	34	14.8%	-7.00 [-18.42, 4.42]	
Rizzo 2008	57	9	11	83	11	11	17.8%	-26.00 [-34.40, -17.60]	_ - _
Total (95% CI)			230			238	100.0%	-21.06 [-28.39, -13.74]	◆
Heterogeneity: Tau ² = 60.21	; Chi ² = :	20.24, df	r= 6 (P	= 0.003	3); I² = 7	0%			-50 -25 0 25 50
Test for overall effect. Z = 5.1	53 (P < U	.00001)							Favours (pre-op IVB) Favours (No IVB)
Study or Subaroup	Pro Mean	e-op IVB SD	Total	Mean	No IVB SD	Total	Weight	Mean Difference IV. Random, 95% Cl	Mean Difference IV. Random, 95% Cl
Arevalo 2019	71.3	32.1	102	83.6	38.7	112	16.1%	-12.30 [-21.80, -2.80]	
di Lauro 2010 El-Batarny 2008	67 61.6	19.45 14.5	48 15	84 93.3	12 11.6	24 15	19.9% 0.0%	-17.00 [-24.30, -9.70] -31.70 [-41.10, -22.30]	
Faisal 2018	64.1	10.35	28	80.5	10.22	28	23.7%	-16.40 [-21.79, -11.01]	
Hernandez-Da Mota 2010 Manabe 2015	62 49	31 20	20 32	98 56	35 27	20 34	5.9% 13.3%	-36.00 [-56.49, -15.51] -7.00 [-18.42, 4.42]	
Modarres 2009	62	57.3	22	95.5	36	18	3.2%	-33.50 [-62.65, -4.35]	
RIZZO 2008	57	9	11	83	11	11	17.9%	-∡o.uu [-34.40, -17.60]	
Total (95% CI)	Chil-	12.00	263	- 0.05	12 - 60	247 «	100.0%	-18.04 [-23.56, -12.51]	◆
Test for overall effect: Z = 6.4	, cn== 40 (P < 0	12.80, ul 1.00001)	= 6 (P	= 0.05)	, 1- = 53	70			-50 -25 0 25 50 Favours (nre-on IVB) Favours (No IVB)
	Pro	e-op IVB		,	ło IVB			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Arevalo 2019 di Lauro 2010	71.3 67	32.1 19.45	102 48	83.6 84	38.7	112	17.0% 19.0%	-12.30 [-21.80, -2.80] -17.00 [-24.30, -9.70]	
El-Batarny 2008	61.6	14.5	15	93.3	11.6	15	17.1%	-31.70 [-41.10, -22.30]	- - -
Faisal 2018 Hernandez-Da Mota 2010	64.1 62	10.35 31	28 20	80.5 98	10.22	28	0.0%	-16.40 [-21.79, -11.01] -36.00 [-56.49, -15.51]	
Manabe 2015	49	20	32	56	27	34	15.2%	-7.00 [-18.42, 4.42]	
Rizzo 2008	62 57	57.3	11	95.5 83	30	18	5.2% 18.0%	-33.50 [-62.65, -4.35] -26.00 [-34.40, -17.60]	
Total (95% CI)			250			234	100.0%	21.30 [.28.8613.75]	•
Heterogeneity: Tau ² = 64.13	; Chi²=	19.18, di	= 6 (P	= 0.004	4); I² = 6	9%			-50 -25 0 25 50
Test for overall effect: Z = 5.	53 (P < 0	.00001)							Favours (pre-op IVB) Favours (No IVB)
Charles - Carl	Pre	e-op IVB	T		lo IVB	T - 4 - 4	187-1-1-4	Mean Difference	Mean Difference
Study of Subdroup	mean	N 11	I OT AL			I OT AL	vveidm		DEAL OF ALL OF A
Arevalo 2019	71.3	32.1	102	83.6	38.7	112	14.9%	-12.30 [-21.80, -2.80]	IV, Random, 95% Cl
Arevalo 2019 di Lauro 2010	71.3	32.1 19.45	102 48	83.6 84	38.7	112 24	14.9%	-12.30 [-21.80, -2.80] -17.00 [-24.30, -9.70]	IV, Random, 95% Cl
Arevalo 2019 di Lauro 2010 El-Batarny 2008 Faisal 2018	71.3 67 61.6 64.1	32.1 19.45 14.5 10.35	102 48 15 28	83.6 84 93.3 80.5	38.7 12 11.6 10.22	112 24 15 28	14.9% 17.6% 15.0% 19.9%	-12.30 [-21.80, -2.80] -17.00 [-24.30, -9.70] -31.70 [-41.10, -22.30] -16.40 [-21.79, -11.01]	IV, Random, 95% Cl
Arevalo 2019 di Lauro 2010 El-Batarny 2008 Faisal 2018 Hernandez-Da Mota 2010 Manaho 2015	71.3 67 61.6 64.1 62	32.1 19.45 14.5 10.35 31 20	102 48 15 28 20	83.6 84 93.3 80.5 98 56	38.7 12 11.6 10.22 35 27	112 24 15 28 20	14.9% 17.6% 15.0% 19.9% 0.0%	-12.30 [-21.80, -2.80] -17.00 [-24.30, -9.70] -31.70 [-41.10, -22.30] -16.40 [-21.79, -11.01] -36.00 [-56.49, -15.51]	V, Kandom, 95% Cl
Arevalo 2019 di Lauro 2010 El-Batarny 2008 Faisal 2018 Hernandez-Da Mota 2010 Manabe 2015 Modarres 2009	71.3 67 61.6 64.1 62 49 62	32.1 19.45 14.5 10.35 31 20 57.3	102 48 15 28 20 32 22	83.6 84 93.3 80.5 98 56 95.5	38.7 12 11.6 10.22 35 27 36	112 24 15 28 20 34 18	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6%	12.30 [-21.80, -2.80] -12.30 [-21.80, -2.80] -17.00 [-24.30, -9.70] -31.70 [-41.10, -22.30] -16.40 [-21.79, -11.01] -36.00 [-56.49, -15.51] -7.00 [-18.42, 4.42] -33.50 [-62.65, -4.35]	N, Kandom, 95% Cl
Arevalo 2019 di Lauro 2010 El-Batarny 2008 Faisal 2018 Hernandez-Da Mota 2010 Manabe 2015 Modarres 2009 Rizzo 2008	71.3 67 61.6 64.1 62 49 62 57	32.1 19.45 14.5 10.35 31 20 57.3 9	102 48 15 28 20 32 22 11	83.6 84 93.3 80.5 98 56 95.5 83	38.7 12 11.6 10.22 35 27 36 11	112 24 15 28 20 34 18 11	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2%	12.30 [-21.80, -2.80] -12.30 [-21.80, -2.80] -17.00 [-24.30, -8.70] -31.70 [-41.10, -22.30] -16.40 [-21.79, -11.01] -36.00 [-56.49, -15.51] -7.00 [-18.42, 4.42] -33.50 [-62.65, -4.35] -26.00 [-34.40, -17.60]	N, Kantom, 95% Cl
Arevaio 2019 di Lauro 2010 El-Batarny 2008 Faisal 2018 Hernandæ-Da Mota 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% CI)	71.3 67 61.6 64.1 62 49 62 57	32.1 19.45 14.5 10.35 31 20 57.3 9	102 48 15 28 20 32 22 11 258	83.6 84 93.3 80.5 98 56 95.5 83	38.7 12 11.6 10.22 35 27 36 11	112 24 15 28 20 34 18 11 242	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0%	12.30 [-21.80, -2.80] -17.00 [-24.30, -9.70] -31.70 [+41.10, -22.30] -16.40 [-21.79, -11.01] -36.00 [-56.49, -15.51] -7.00 [-18.42, 4.42] -33.50 [-62.65, -4.35] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14]	
Arevalo 2019 di Lauro 2010 El-Batarny 2008 Faisal 2018 Hermandez Da Mota 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% CI) Heterogeneiky: Tau ² = 39.89 Test for overall effect Z = 6	71.3 67 61.6 64.1 62 49 62 57 ; Chi ² = - 24 (P < 0	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, dt	102 48 15 28 20 32 22 11 258 5 = 6 (P	83.6 84 93.3 80.5 98 56 95.5 83	38.7 12 11.6 10.22 35 27 36 11	112 24 15 28 20 34 18 11 242 7%	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0%	12.30 [-21.80, -2.80] -17.00 [-24.30, -87.00] -31.70 [+41.10, -22.30] -16.40 [-21.79, -11.01] -36.00 [-56.49, -15.51] -7.00 [-18.42, 4.42] -33.50 [-62.65, -4.35] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14]	N, Kandom, 95% Cl
Arevalo 2019 di Lauro 2010 El-Batarny 2008 Faisal 2018 Hernandez-Da Mota 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% CI) Heterogeneity: Tau ^a = 39.88 Test for overall effect. Z = 6.:	71.3 67 61.6 64.1 62 49 62 57 ; Chi ² = - 24 (P < 0	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, dt .00001)	102 48 15 28 20 32 22 11 258 5= 6 (P	83.6 84 93.3 80.5 98 56 95.5 83	38.7 12 11.6 10.22 35 27 36 11 3); ² = 6	112 24 15 28 20 34 18 11 242 7%	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2%	V, Raitoni, 35% Cl. 12.30 (-21.80, -2.80) -17.00 (-24.30, -8.70) -31.70 (-41.10, -22.30) -16.40 (-21.79, -11.01) -36.00 (-56.49, -15.51) -7.00 (-18.42, 4.42) -3.50 (-62.65, -4.36) -26.00 (-34.40, -17.60) -19.16 (-25.19, -13.14)	N, Kandom, 95% Cl
Arenica 2019 Arenica 2010 El-Batarry 2008 Faisal 2018 Hermandez-Da Mola 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% CI) Heterogeneik, Tau ² = 39.89 Test for overall effect Z = 6 Study or Subgroup	71.3 67 61.6 64.1 62 49 62 57 ; Chi₹ = 1 24 (P < 0 Pro Mean	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, dt 1.00001) e-op IVB SD	102 48 15 28 20 32 22 11 258 5 = 6 (P	83.6 84 93.3 80.5 98 56 95.5 83 •= 0.008	38.7 12 11.6 10.22 35 27 36 11 36 11 30); I ² = 6 No IVB SD	112 24 15 28 20 34 18 11 242 7% Total	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0%	12.30 [-21.80, -2.80] -17.00 [-24.30, -2.80] -17.00 [-24.30, -8.70] -31.70 [-41.10, -22.30] -16.40 [-21.73, -11.01] -36.00 [-56.49, -15.51] -7.00 [-18.42, 4.42] -36.00 [-52.65, -4.36] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14] Mean Difference V, Random, 95% C1	N, Kandom, 95% Cl
Arevalo 2019 Arevalo 2010 El-Batarny 2008 Faisal 2018 Hermandez-Da Mola 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% CI) Heterogeneth; Tau ² = 39.88 Test for overall effect Z = 6. <u>Study or Subgroup</u> Arevalo 2019 di Lauro 2010	71.3 67 61.6 64.1 62 49 62 57 ; Chi ² = - 24 (P < 0 <u>Pro</u> <u>Mean</u> 71.3 67	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, dt .00001) e-op IVB SD 32.1 19.45	102 48 15 28 20 32 22 11 258 5= 6 (P Total	83.6 84 93.3 80.5 98 56 95.5 83 = 0.000 Mean 83.6	38.7 12 11.6 10.22 355 27 36 11 5); I ² = 6 No IVB SD 38.7 12 36 11 37 36 37 36 37 36 37 36 37 36 37 36 37 36 37 36 38 37 36 37 36 38 37 36 38 37 36 38 37 36 38 37 36 38 37 36 38 38 38 38 38 38 38 38 38 38	112 24 15 28 20 34 18 11 242 7% Total	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0% Weight 15.9%	12.30 [-21.80, -2.80] -17.00 [-24.30, -2.80] -17.00 [-24.30, -8.70] -31.70 [-41.10, -22.30] -16.40 [-21.79, -11.01] -70.00 [-18.42, 4.42] -33.50 [-55.65, -4.35] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14] Mean Difference V. Random, 95% C1 -12.30 [-21.80, -28.00]	N, Kandom, 95% Cl
Arevalo 2019 Arevalo 2010 El-Batarry 2000 Faisal 2018 Hermandez-Do Mota 2010 Manabe 2015 Modarres 2000 Rizzo 2008 Total (95% CI) Heterogenety, Tau* = 39.88 Test for overall effect Z = 6. <u>Study of Subgroup</u> Arevalo 2019 di Lauo 2010 El-Batarry 2008	71.3 67 61.6 64.1 62 49 62 57 ; Chi ² = - 24 (P < 0 <u>Pro</u> <u>Mean</u> 71.3 67 61.6	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, df 100001) 50 32.1 19.45 14.5	102 48 15 28 20 32 22 11 258 5= 6 (P Total 102 48 15	83.6 84 93.3 80.5 98 56 95.5 83 *= 0.006 Mean 83.6 84 93.3	SD 38.7 12 11.6 10.22 35 27 36 11 5); ₱ = 6 No IVB SD 38.7 12 38.7 12 38.7 12 38.7 12 38.7 12	112 24 28 20 34 18 11 242 7% Total 112 24 24 15	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0% Weight 15.9% 18.9% 16.0%	IV, Randolf, 35% CI 12.30 [-2180, -2.80] -17.00 [-24.30, -8.70] -31.70 [-41.10, -22.30] -16.40 [-21.78, -11.01] -70.00 [-18.42, 4.42] -35.50 [-55.43] -35.50 [-55.43] -35.60 [-55.54, -35] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14] Mean Difference IV, Random, 95% CI -12.30 [-21.80, -2.80] -17.00 [-24.30, -2.70]	N, Kandom, 95% Cl
Arevice 2019 di Lauro 2010 El-Batarry 2008 Paisal 2010 Hernandez-Da Mota 2010 Maraba 2010 Motarres 2009 Rizzo 2008 Todal (95% C) Heterogenety, Tau" = 38.89 Test for overall effect Z = 6. Study or Subgroup Arevice 2019 di Lauro 2010 El-Batarry 2008 Faisal 2018 Hernandez-Da Mota 2019	71.3 67 61.6 64.1 62 49 62 57 ; Chi ² = - 24 (P < 0 Pro <u>Mean</u> 71.3 67 61.6 64.1 <i>p</i>	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, dt 000001) 2-0p IVB SD 32.1 19.45 14.5 10.35 31	102 48 15 28 20 32 22 11 258 5 = 6 (P Total 102 48 15 28 20 32 22 21 11	83.6 84 93.3 80.5 98 56 95.5 83 '= 0.000 1000 Mean 83.6 84 93.3 80.5 98 2000 1000	38.7 12 11.6 10.22 35 27 36 11 35 27 36 11 35 27 36 11 35 27 36 11 36 11 10.22 35 27 36 11 1.16 10.22 35 27 36 11 1.16 10.22 35 27 36 11 1.16 10.22 35 27 36 11 11 36 11 35 27 36 11 11 36 11 38 38 11 38 38.7 11 38 38.7 12 11 36 11 38.7 12 11 36 11 38.7 38.7 12 38.7 12 38.7 12 38.7 12 38.7 12 11.6 10.22 38.7 12 11.6 10.22 38.7 10.22 38.7 10.22 38.7 10.22 38.7 10.22 38.7 10.22 38.7 10.22 38.7 10.22 38.7 10.25 10.25 10.25 10.25 10.55 10.25 10.55 10	112 28 20 34 18 11 242 7% Total 112 24 15 24 24 5 22 24 25 20	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0% Weight 15.9% 18.9% 16.0% 21.7% 6.5%	IV, Raitolin, 35% CI 12.30 [2180, 2.80] -17.00 [24.30, -870] -31.70 [4-11.02.230] -16.40 [21.79, -11.01] -70.00 [18.42, 442] -35.60 [56.46, -15.51] -36.00 [56.43, -17.60] -19.16 [-25.19, -13.14] Mean Difference IV, Random, 95% CI -17.00 [24.30, -870] -17.00 [24.30, -870] -17.00 [24.30, -870] -17.00 [24.30, -870] -16.40 [21.79, -11.01] -36.00 [4.45.51]	N, Kandom, 95% Cl
Arevice 2019 di Lauro 2010 El-Batarry 2000 Hernandez Da Mota 2010 Manabe 2015 Modarres 2009 Rizz 2008 Test for overall effect. 2 = 6. Study or Subgroup Arevice 2019 di Lauro 2010 El-Batarry 2000 Hernandez Da Mota 2010 Manabe 2015.	71.3 67 61.6 64.1 62 49 62 57 24 (P < 0 24 (P < 0 71.3 67 61.6 64.1 71.3 67 61.6 64.1 71.3	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, dt 100001) 32.1 19.45 10.35 32.1 19.45 10.35 31 20 57.3 32 57.3 9 57.3 10.45 57.3 9 57.3 10.45 57.3 9 57.3 10.45 10.45 10.45 10.45 10.45 10.3	102 48 20 32 22 11 258 Total 102 56 (P Total 102 48 15 28 20 32 22 21	83.6 84 93.3 80.5 98 56 95.5 83 = 0.006 1000 Mean 83.6 84 93.3 80.5 98 56 98 56 98 50 98 98 93.3 80.5 98 56 98 56 98 56 98	38.7 12 11.6 10.22 35 27 36 11 30; ₹ = 6 No IVB SD 38.7 12 38.7 12 11.6 10.22 35 27 36 11 35 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 36 11 27 38 27 38 27 36 11 28 27 38 27 38 27 38 28 27 38 28 27 38 38.7 12 27 38.7 12 11 12 27 38.7 12 11 12 27 38.7 12 11 10.22 35 27 38.7 12 11.6 10.22 35 27 38.7 12 11.6 10.22 35 27 38.7 12 11.6 10.22 35 27 38.7 12 11.6 10.22 35 27 12 11.6 10.22 35 27 11.6 10.22 35 27 11.6 10.22 35 27 11.6 10.22 35 27 11.6 10.22 35 27 27 11.6 10.52 27 27 12 27 27 27 27 27 27 27 27 27 2	112 24 15 28 20 34 18 11 242 7% Total 112 24 24 15 28 20 34 15 28 20 34 34 34 34 34 34 34 34 34 34 34 34 34	14.9% 17.6% 15.0% 19.9% 12.8% 3.6% 16.2% 100.0% 15.9% 18.9% 16.0% 21.7% 6.5% 0.0%	IV, Rationi, 359-CI 12.30 (24.80, -2.80) -17.00 (24.30, -8.70) -17.00 (24.30, -8.70) -17.00 (24.30, -8.70) -16.40 (22.78, -11.01) -7.00 (-18.42, 4.42) -28.50 (-25.6, -4.35) -28.50 (-25.43, -15.51) -7.00 (-18.44, -17.60) -19.16 (-25.19, -13.14) Mean Difference IV, Random, 95% CI -17.30 (-21.80, -8.70) -17.00 (-24.30, -9.70) -17.00 (-24.30, -9.70) -17.00 (-24.30, -9.70) -17.00 (-56.42, -11.01) -7.00 (-56.42, -11.01) -7.00 (-56.42, -14.2)	N, Kantom, 95% Cl
Arevalo 2019 Arevalo 2019 E-batamy 2008 Faisal 2018 Hermandes: Do a Mota 2010 Manabe 2015 Modarres 2009 Total (95% CI) Heterogeneity: Tau* = 39.89 Test for overall effect 2 = 6: <u>Study or Subgroup</u> Arevalo 2019 di Lauro 2010 E-Batamy 2008 Hermandes: Do a Mota 2010 Menabe 2015 Modarres 2009 Rizzo 2008	71.3 67 61.6 64.1 62 49 62 57 24 (P < 0 Pro Mean 71.3 67 61.6 64.1 62 49 62,57	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, df 100001) 32.1 19.45 14.5 10.35 32.1 19.45 14.5 10.35 32.1 19.45 14.5 10.35 32.1 20 57.3 9 32.1 19.45 10.35 32.1 20 57.3 9 32.1 20 57.3 9 32.1 20 57.3 9 32.1 10.0001) 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.0001 32.1 10.005 10.0001 32.1 10.005 10.005 10.0001 32.1 10.005 10.005 10.005 10.005 10.005 10.005 10.005 10.005 10.005 10.005 10.005 10.005 10.05	102 102 48 15 28 20 32 22 11 258 5 6 (P Total 102 48 15 28 20 32 22 11	Niedaii 83.6 84 93.3 80.5 98 96 95.5 83 = 0.000 1 Mean 83.6 84 93.3 80.5 98 56 83 80.5 98 86.5 84 93.6 84 95.5 98 56 83	38.7 38.7 12 11.6 10.22 35 27 36 11 11 35 ; I ² = 6 SD 38.7 12 11.6 10.22 35 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 36 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 38 5 27 28 5 27 38 5 27 28 5 27 38 5 27 27 28 5 27 28 5 27 28 28 5 27 38 5 7 22 21 11 11 11 11 11 11 11 11	112 24 15 28 20 34 18 11 242 7% Total 112 242 27% Total 112 24 24 15 28 20 34 115 28 20 34 115 28 20 34 115 28 20 34 115 28 20 34 24 24 24 24 24 24 24 24 24 24 24 24 24	14.9% 14.9% 17.6% 15.0% 19.9% 12.8% 3.6% 16.2% 100.0% Weight 15.9% 18.9% 16.0% 21.7% 6.5% 0.0% 3.7% 17.4%	IV, Randolf, 35% CI 12.30 (2180, 280) -17.00 (24.30, -870) -17.00 (24.30, -870) -31.70 (4-11.0, -22.30) -16.40 (21.78, -11.01) -35.00 (56.48, -15.51) -35.00 (56.48, -15.51) -35.00 (26.56, -4.38) -26.00 (34.40, -17.60) -19.16 (-25.19, -13.14) Mean Difference IV, Random, 95% CI -17.30 (24.30, -870) -17.00 (24.30, -870) -17.00 (24.30, -870) -17.00 (56.49, -11.01) -36.00 (56.42, -14.2) -26.00 (34.42, 4.42) -30.0 (56.44, -17.60)	N, Kandom, 95% Cl
Arevice 2019 Arevice 2010 El-Batarry 2008 Faisal 2010 El-Batarry 2008 Faisal 2018 Memandez 2015 Modarres 2009 Total (95% CI) Heterogeneiky, Tau ² = 39.89 Test for overall effect Z = 6.3 Study or Subgroup Arevice 2019 di Laure 2010 El-Batarry 2008 Hemandez Da Mola 2010 Manabe 2018 Hemandez Da Mola 2010 Manabe 2018 Hemandez Da Mola 2010 Manabe 2018 Hemandez Da Mola 2010 Rizzo 2008 Rizzo 2008	71.3 67 61.6 64.1 62 49 62 57 24 (P < 0 Pro Mean 71.3 67 61.6 64.1 62 49 62 57	32.1 19.45 14.5 10.35 31 20 57.3 9 9 17.93, dt 0.00001) 9 57.3 32.1 19.45 50 32.1 19.45 10.35 31 20 57.3 9 9 32.1 19.5 57.3 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	102 102 48 15 28 20 32 22 11 258 5 = 6 (P Total 102 48 15 28 20 32 22 11 102 48 15 28 20 32 22 11 102 48 48 15 28 20 32 22 11 258 20 32 22 11 258 20 32 22 11 258 20 32 22 11 258 20 32 22 11 258 20 32 22 11 258 20 32 22 11 258 20 32 22 11 258 20 32 22 21 11 258 20 32 22 21 11 258 20 32 22 21 21 21 21 21 21 21 21 21 21 21 21	Nean 83.6 84 93.3 80.5 98 56 95.5 83 98 83.6 98.6 84 93.3 80.5 98 83.6 94.5 98 98.0 93.3 80.5 98 96.5 83 96.5 83	SD 38.7 12 11.6 10.22 35 27 36 11 50; IP = 6 SD 38.7 12.6 10.22 38.7 12.3 12.4 10.22 35 27 36 11.1	112 24 15 28 20 34 18 11 242 24 15 24 112 24 15 28 20 34 112 24 15 28 20 4 15 28 112 24 112 24 20 24 15 24 20 24 20 24 20 24 24 24 24 24 24 24 24 24 24 24 24 24	14.9% 14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0% Weight 15.9% 18.9% 18.9% 16.0% 21.7% 6.5% 0.0% 3.7% 17.4% 100.9%	IV, Randolf, 35% CI 12.30 [2180, 280] -17.00 [24.30, -280] -17.00 [24.30, -270] -31.70 [4-11.02.230] -16.40 [21.78, -11.01] -7.00 [18.42, 442] -35.50 [25.64, -15.51] -35.50 [25.65, -4.35] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14] Mean Difference V, Random, 95% CI -17.00 [24.30, -9.70] -31.70 [-41.00, -28.00] -36.00 [-56.44, -15.51] -70.0 [-18.42, 442] -70.0 [-18.42, 442] -36.0 [-56.43, -9.70] -31.70 [-41.10, -22.30] -32.60 [-54.42, -17.50] -33.70 [-44.42, 442] -33.60 [-52.65, -435] -26.00 [-54.40, -17.50] -26.00 [-54.40, -17.50] -26.00 [-54.40, -17.50]	N, Kandom, 95% Cl
Arevalo 2019 Arevalo 2010 EI-Batarny 2000 Faisal 2018 Hermandez-Da Mola 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% CI) Heterogenehy, Tau ² = 39.89 Test for overall effect Z = 6. <u>Study or Subgroup</u> Arevalo 2019 di Lauro 2010 EI-Batarny 2008 Faisal 2018 Hermandez-Da Mola 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% CI) Heterogenehy, Tau ² = 38.07	71.3 67 61.6 64.1 62 49 62 57 71.3 67 71.3 67 71.3 67 71.3 67 71.3 61.6 64.1 62 99 62 57 7 61.6 64.1 62 99 62 57	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, dt 17.93, dt 17.93, dt 17.93, dt 19.45 10.0001) 32.1 19.45 10.35 31 20 57.3 9 9	102 102 48 15 28 20 32 22 211 258 5 6 (P Total 102 48 102 48 102 48 20 32 22 11 102 48 20 32 22 11 102 48 20 32 22 11 102 48 20 32 22 11 102 48 20 32 22 11 102 48 20 32 22 21 11 102 48 20 32 22 21 11 102 48 20 32 22 21 11 102 48 20 102 102 102 102 102 102 102	Netan 83.6 84 93.3 80.5 98 56 95.5 83 = 0.000 Mean 83.6 84 93.3 80.5 84 93.3 80.5 98 96 95.5 83 96.5 93.3 80.5 98 96.5 93.3 98.5 95.6 83 95.6 98 98 98 98 98 98 98.5 98.3 98 98 98 98 98 98 98 98 98 98 98 <	str str 38.7 12 11.6 10.22 35.7 27 36 11 30); I*= 6 6 SD 38.7 11.6 10.22 36 11 SD 38.7 12 11.6 10.22 35 27 36 11.2 27 36 11 () F= 62 27 36 11	112 24 15 28 20 34 18 11 242 7% Total 112 24 15 28 20 34 15 28 20 34 15 28 28 20 34 52 8 20 34 52 8 20 53 52 8 20 53 54 55 52 8 52 8 52 70 55 70 55 70 55 70 55 70 55 70 55 70 55 70 70 70 70 70 70 70 70 70 70 70 70 70	14.9% 17.6% 17.6% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0% 15.9% 18.9% 16.0% 21.7% 6.5% 0.0% 3.7% 17.4%	IV, Randolf, 35% CI 12.30 [2180, 280] -17.00 [24.30, -870] -17.00 [24.30, -870] -31.70 [4-11.022.30] -16.40 [21.73, -11.01] -7.00 [18.42, 442] -35.50 [25.64, -15.51] -35.50 [25.65, -4.36] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14] Mean Difference IV, Random, 95% CI -17.00 [-24.30, -9.70] -31.70 [+1.10, -22.30] -16.40 [-21.73, -11.01] -35.00 [-34.40, -15.51] -70.00 [-34.42, 442] -35.00 [-56.5, -4.35] -35.00 [-56.5, -4.36] -26.00 [-34.40, -17.60] -28.00 [-34.40, -17.60] -28.00 [-34.40, -17.60] -28.00 [-34.40, -17.60]	N, Kandom, 95% Cl
Arevice 2019 di Lauro 2010 El-Batarry 2008 Falisal 2010 Hernandez Da Mola 2010 Maraba 2016 Modarnes 2009 Rizzo 2008 Todal (95% C) Heterogeneely, Tau ⁺ = 39.89 Test for overall effect Z = 6: Study or Subgroup Arevice 2019 di Lauro 2010 El-Batarry 2008 Falisal 2018 Hernandez-Da Mola 2010 Maraba 2015 Rodarnes 2009 Rizzo 2008 Todal (95% C) Heterogenety, Tau ⁺ = 36.07 Test for overall effect Z = 7:	71.3 67 61.6 64.1 62 99 62 57 7 7 1.3 67 61.6 64.1 62 9 9 7 1.3 67 61.6 64.1 62 9 9 9 7 1.3 67 7 1.3 67 7 1.3 67 7 1.5 7 7 1.5 8 7 7 1.5 8 7 7 8 1.6 8 1.5 7 7 8 1.6 8 1.5 7 7 8 1.6 8 1.5 7 7 8 1.6 8 1.5 7 7 8 1.6 8 1.5 7 7 8 1.6 8 1.5 7 7 7 1.5 8 1.5 7 7 7 1.5 8 1.5 7 7 7 1.5 8 1.5 7 7 8 1.5 7 7 7 1.3 8 7 7 1.3 8 7 7 1.5 7 7 1.3 8 7 7 1.3 8 7 7 1.3 8 7 7 1.3 8 7 7 1.3 8 7 7 1.3 7 7 7 1.3 7 7 7 1.3 8 7 7 1.3 8 7 7 7 7 7 1.3 8 7 7 7 1.3 7 7 7 7 1.3 7 7 7 7 1.3 8 7 7 7 1.5 7 7 7 7 7 7 8 1.5 7 7 7 7 7 7 7 8 1.6 8 7 7 7 7 8 7 7 7 7 7 7 8 1.6 8 7 7 7 7 7 7 7 8 7 8 7 8 7 7 8 7 7 7 7 7 8 1.5 7 7 7 7 8 1.5 7 7 7 7 8 7 8 7 7 8 7 8 7 7 7 7 8 1.6 7 7 7 7 7 7 8 1.6 7 7 7 7 7 7 8 1.6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	32.1 19.45 14.5 10.35 31 20 57.3 9 9 17.93, dt 10.0001) 32.1 19.45 32.1 19.45 31 14.5 10.35 31 14.5 31 14.5 57.3 9 9	102 48 15 28 20 32 22 11 258 6 (P Total 102 48 15 28 20 32 22 11 102 48 15 28 20 32 22 11 246 6 (P	Nitean 83.6 84 93.3 80.5 98 98 56 95.5 83 98 56 95.5 83 98 80.5 83 98 80.5 98.3 80.5 98.3 80.5 98 86.5 98.5 83 96.5 83 95.5 95.5 83 95.	str str 38.7 12 11.6 10.22 35.7 27 36.6 11 50; I*= 6 50 38.7 12 11.6 50; I*= 6 10.22 35 38.7 12 11.6 10.22 35 77 36 11 (; I*= 62	112 24 15 28 20 34 18 11 242 7% Total 112 24 24 15 28 20 34 15 28 20 34 15 28 20 34 15 28 20 34 5 5 28 20 34 5 5 5 8 28 5 28 28 20 34 34 15 5 28 28 28 28 28 28 28 28 28 28 28 28 28	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 16.2% 100.0% 15.9% 16.0% 21.7% 6.5% 0.0% 3.7% 17.4%	IV, Randoff, 30%-C1 12.30 [2:10, 2:80] -17.00 [2:4.30, -8.70] -17.00 [2:4.30, -8.70] -31.70 [4:1.0, 2:2.30] -16.40 [2:1.78, -11.01] -70.00 [18.42, 14.2] -35.50 [2:65, 4:35] -35.60 [2:65, 4:36] -35.60 [2:65, 4:36] -26.00 [34.40, -17.60] -19.16 [-25.19, -13.14] Mean Difference IV, Random, 95% [1 -12.30 [2:1.80, -2.80] -17.00 [2:4.30, -2.70] -35.00 [2:64, -10, -2.70] -35.00 [2:65, -4.35] -35.00 [2:65, -4.35] -35.00 [2:65, -4.35] -35.00 [2:65, -4.35] -35.00 [2:65, -4.35] -26.00 [3:4.40, -17.60] -28.00 [3:4.40, -17.60] -21.88 [-27.91, -15.86]	N, Kandom, 95% Cl
Arevice 2019 di Lauro 2010 El-Batarry 2000 Hernandez Da Mota 2010 Manabe 2016 Hernandez Da Mota 2010 Manabe 2016 Ritze 2008 Total (95% C) Heterogeneily, Tau ² = 39.89 Test for overall effect. 2 = 6; Study or Subgroup Arevice 2019 di Lauro 2010 El-Batarry 2000 El-Batarry 2000 Hernandez Da Mota 2010 Modarnes 2009 Total (95% C) Heterogeneily, Tau ² = 36.07 Test for overall effect. 2 = 7; Charabe 2015	71.3 67 61.6 64.1 62 49 62 57 7 7 7 7 7 7 7 7 7 7 7 61.6 64.1 62 49 9 7 7 1.3 67 61.6 64.1 22 4 9 9 62 57 7 7 1.3 67 7 1.3 7 7 1.3 7 7 1.3 7 7 7 1.3 7 7 7 7 7 7 1.3 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	32.1 19.45 14.5 10.35 31 20 57.3 9 17.93, dt 19.45 10.35 32.1 19.45 14.5 5 10.35 32.1 19.45 10.35 31 19.45 10.35 31 19.45 10.35 32.1 19.45 10.35 32.1 19.45 10.35 32.1 19.45 10.35 32.1 19.45 10.35 32.1 19.45 10.35 10.	102 48 15 28 20 32 22 11 258 5 6 (P Total 102 48 15 28 20 32 22 11 102 48 20 32 22 11 246 6 (P	Nitean 83.6 84 93.3 80.5 98 98 56 95.5 83 98 56 95.5 83 98 83.6 84.4 93.3 80.5 98.3 80.5 98.3 80.5 98.3 80.5 98.3 80.5 98.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.3 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5 83.4 80.5	stor 38,7 12 11.6 10.22 35 27 36 11 50; P = 6 No IVB SD 38,7 12 38,7 12 38,7 12 38,7 12,10 38,7 12,21 10,022 35 27 36 11 10,022 35 27 36 11 ; P = 62 No IVB	112 24 15 28 20 34 18 11 242 7% Total 112 24 15 28 20 34 15 28 20 34 15 28 %	14,9% 17,6% 15,0% 19,9% 0,0% 12,8% 28,8% 16,2% 100,0% 16,2% 100,0% 16,0% 21,7% 16,5% 0,0% 3,7% 17,4%	Nr. Ration, 307-61. 12.30 (214) 230 (230) 17.0 (4-1) 22.30) 13.70 (4-1) 22.30) 16.40 (21.78, -11.01) -7.00 (-18.42, 4.42) 23.50 (-25.64, -15.51) -7.00 (-18.42, 4.42) -3.50 (-25.65, -4.35) -28.00 (-34.40, -17.60) -19.16 (-25.19, -13.14) Mean Difference Mr. Random, 95% C1 -17.00 (-24.30, -8.70) -17.00 (-24.30, -9.70) -31.70 (+41.00, -22.30) -35.00 (-56.44, -15.51) -7.00 (-18.42, 4.42) -26.00 (-34.40, -17.60) -26.00 (-34.40, -17.60) -26.00 (-54.42, -17.50) -28.00 (-24.40, -17.60) -26.00 (-24.40, -17.60) -21.88 (-27.91, -15.86)	N, Kandom, 95% Cl
Arevalo 2019 Arevalo 2019 E-batamy 2008 Faisal 2019 E-batamy 2008 Faisal 2019 Modares 2009 Total (95% C1) Heterogenety: Tau ² = 38.89 Test for overall effect 2 = 6: <u>Study or Subgroup</u> Arevalo 2019 di Lauro 2010 E-batamy 2008 Total (95% C1) Heterogenety: Tau ² = 36.07 Test for overall effect 2 = 7: <u>Study or Subgroup</u> Arevalo 2019	71.3 67 61.6 64.1 62 49 62 57 7 1.3 67 61.6 64.1 7 71.3 67 61.6 64.1 62 49 62 57 7 1.6 64.1 62 49 62 57 7 1.2 67 61.6 64.1 7 7 61.6 6 7 7 7 61.6 6 9 62 62 62 7 7 7 7 61.6 6 7 62 62 62 62 62 62 7 7 7 7 7 61.6 6 8 62 7 7 7 7 7 61.6 6 7 7 7 7 7 7 7 7 6 7 6 7 7 7 7 7 7 7	32.1 19.45 14.5 10.35 31 20 57.3 9 9 17.93, dt 17.93, dt 17.93, dt 17.93, dt 19.45 10.35 32.1 19.45 10.35 31 20 57.3 9 9 15.97, dt 10.35 32.1 19.45 10.35 32.1 19.45 10.35 32.1 19.45 10.35 32.1 19.45 10.35 32.1 19.45 10.35	102 48 15 28 20 32 22 11 258 56 (P Total 102 48 15 28 20 32 22 11 102 48 15 28 6 (P Total 102 48 15 28 6 (P Total 102 48 15 28 20 20 22 21 10 25 28 20 20 20 20 20 20 20 20 20 20 20 20 20	Nean 83.6 84 93.3 80.5 98 96 95.5 83 8 96 95.5 83 8 98 8 98 96 98 96 98 96 99 95.5 83 80.5 98 96 99 95.5 83 80.5 98 96 99 95.5 83 80.5 98 96.5 83 80.5 98 96.5 83 80.5 83 80.5 83 80.5 83 80.6 83 83.6	stor 38.7 12 11.6 10.22 35 27 36 11 50; F = 6 36 11 10.22 38.7 12 11.6 10.22 36 11 10.22 36 11 (; F = 62 40 IVB SD 38.7	112 24 152 28 20 34 18 11 242 7% Total 112 24 24 25 28 20 34 112 242 24 25 28 20 34 112 242 24 52 8 20 34 112 24 24 52 8 20 34 112 24 20 34 112 24 20 34 112 24 20 34 112 24 20 34 112 24 20 34 112 20 20 34 112 20 20 20 34 112 20 20 20 34 112 20 20 20 20 34 112 20 20 20 20 20 20 20 20 20 20 20 20 20	14,9% 17,6% 15,0% 15,0% 19,9% 0,0% 12,8% 3,6% 16,2% 100,0% Weight 10,0% 10	Nr. Randoff, 30%-CI. 12.30 [2180, 2.80] -17.00 [24.30, -870] -17.00 [24.30, -870] -31.70 [4-11, -22.30] -16.40 [21.78, -11.01] -35.00 [25.64, -15.51] -35.00 [25.64, -15.51] -35.00 [25.65, -4.38] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14] Mean Difference W, Random, 95% CI -17.30 [24.30, -870] -17.00 [24.30, -870] -17.00 [24.30, -870] -17.00 [24.30, -870] -17.00 [24.30, -870] -17.00 [24.30, -870] -17.00 [24.42, 4.42] -26.00 [54.40, -17.60] -26.00 [54.40, -17.60] -26.00 [54.40, -17.60] -26.00 [54.40, -17.60] -26.00 [54.40, -17.60] -26.00 [54.40, -17.60] -26.00 [54.40, -17.60] -21.88 [-27.91, -15.86] Mean Difference W, Random, 95% CI -12.30 [21.80 - 2.80]	N, Kandom, 95% Cl
Arevalo 2019 Arevalo 2019 E-Batamy 2008 Faisa 12018 Hermandez-Da Mota 2010 Manabe 2015 Modarres 2009 Total (95% CI) Heterogenethy, Tau* = 39.89 Test for overall effect Z = 6. Study or Subgroup Arevalo 2019 di Lauro 2010 E-Batamy 2008 Total (95% CI) Heterogenethy, Tau* = 36.07 Test for overall effect Z = 7. Study or Subgroup Arevalo 2019 di Lauro 2010 E-Batamy 2008 Total (95% CI) Heterogenethy, Tau* = 36.07 Test for overall effect Z = 7. Study or Subgroup Arevalo 2019 di Lauro 2019	71.3 67 61.6 64.1 62 49 62 57 7 1.3 67 61.6 64.1 7 7.1.3 67 61.6 64.1 62 49 9 62 57 7 1.3 67 7 61.6 64.1 7 7 1.3 67 7 7 61.6 6 9 7 7 7 8 7 6 7 6 7 6 7 6 7 6 7 6 7 6 7 6	32.1 19.45 14.5 31 10.35 31 0.05 57.3 9 9 17.93, dt 0.00001) so 7.9, f 10.35 so 7.9, f 10.35 so 7.9, f 10.35 so 7.3 9 9 32.1 10.95 so 7.3 9 9 32.1 10.95 so 7.3 9 9 9 17.93, dt 10.95 so 7.3 9 9 17.93, dt 10.95 so 7.3 9 9 17.93, dt 10.95 so 7.3 9 9 17.93, dt 10.95 so 7.3 9 9 17.93, dt 10.95 so 7.3 9 9 17.93, dt 10.95 so 7.3 9 10.95 so 7.3 9 10.95 so 7.3 9 10.95 so 7.3 9 10.95 so 7.3 9 10.95 so 7.3 10.95 so 7.3 9 10.95 so 7.3 9 10.95 so 7.95 10.95 so 7.95 10.95	102 48 15 28 20 32 22 11 258 56 (P Total 102 48 15 28 20 10 246 52 8 20 32 22 21 10 246 52 8 52 8 52 8 52 8 52 53 52 54 52 55 52 54 52 52 52 52 52 52 52 52 52 52 52 52 52	Notes 83.6 84 84 98.3 80.5 98 96 99.5 83 99.5 83 99.5 83 99.6 83.6 98.8 98.8 96.5 83 99.5 83.8 90.011 96.5 83.6 83.6 96.5 83 96.5 83 96.5 83 96.5 83 96.5 83 97.5 83 98.8 80.6 99.5 83 99.5 83 90.5 83 90.5 83 90.5 83 90.5 83 90.5 83 90.5 83 90.6 84 90.7 90.7	sol sol 38.7 12 11.6 10.22 35 27 36 11 50); F = 6 11 50; F = 62 38.7 11.6 10.22 11.6 10.22 35.7 36.7 10.22 35 277 36 11 11.6 VP = 622 38.7 38.7 38.7 12 11.6 50 38.7 12 12.6 38.7 12.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 12.2	112 24 152 28 20 34 18 11 242 7% Total 112 24 24 26 34 112 242 7% Total 112 24 28 20 34 111 242 7% Total 112 24 24 26 20 34 112 24 20 34 112 24 20 34 112 24 20 34 112 20 20 34 112 20 20 34 112 20 20 34 112 20 20 34 112 20 20 34 112 20 20 34 112 20 20 20 34 112 20 20 20 34 112 20 20 20 34 112 20 20 20 34 112 20 20 20 34 112 20 20 20 34 112 20 20 20 20 20 20 20 20 20 20 20 20 20	14.9% 17.6% 15.0% 19.9% 0.0% 12.8% 3.6% 16.2% 100.0% Weight 10.0% 10.0% 14.6% 10.0% 17.4% 100.0% 17.4% 10.0% 17.6% 10.0% 1	IV, Raitoni, Sov. 2.80; 12.30 [2:18,07, 2:180; -17.00 [2:43,0], -27.01; -31.70 [4:11,022,30] -16.40 [2:1.78, -11.01]; -35.00 [5:64, -15.51]; -7.00 [1:8,42, 442]; -33.50 [2:65, -4.35]; -26.00 [3:4,40, -17.60]; -19.16 [-25.19, -13.14]; Mean Difference VK, Random, 95% C1 -12.30 [2:18,0], -28.01; -17.00 [-43,0], -70.01; -33.60 [-56,43]; -26.00 [-34.40, -17.60]; -12.30 [-21.80, -28.01; -12.30 [-21.80, -28.01; -12.30 [-21.80, -28.01; -26.00 [-34.40, -17.60]; -21.38 [-27.91, -15.86]; Mean Difference VK, Random, 95% C1 -12.30 [-21.80, -28.01; -12.30 [-24.30, -8.70]; -12.30 [-24.30, -8.70];	N, Kandom, 95% Cl
Arevia 0219 Arevia 0219 di Lauro 2010 El-Batarry 2008 Hemandez-Da Motă 2010 Marabe 2016 Motarres 2009 Rizzo 2008 Toda (95% C) Heterogeneity, Tau ² = 38.89 Test for overail effect Z = 6.1 Study or Subgroup Arevia 0210 El-Batarry 2008 Faisal 2018 Motarres 2009 Rizzo 2008 Tota (95% C) Heterogeneity, Tau ² = 36.07 Test for overail effect Z = 7.1 Study or Subgroup Arevia 0210 El-Batarry 2008 Rizzo 2018 di Lauro 2010 El-Batarry 2010 El-Batarry 2018	71.3 67 61.6 64.1 62 49 62 57 57 57 71.3 67 61.6 64.1 64.1 64.1 64.1 64.1 64.1 64.1	32.1 19.45 14.5 31 10.35 31 0.00001) 57.3 9 17.93, dt 0.00001) 32.1 19.45 31 10.35 31 14.5 31 10.35 57.3 9 9 50, 00001) 9 50, 00001) 9 50, 00001 19.45 51, 000001 19.45 51, 00001 19.45 51, 00001 19.55 51, 000000000000000000000000000000000000	102 48 15 28 20 32 22 21 11 258 5 = 6 (P Total 102 48 20 32 22 11 102 48 20 32 22 11 246 6 (P Total 102 48 15 28 20 20 21 11 102 48 48 15 5 = 6 (P Total 102 48 15 28 20 20 21 11 102 48 48 15 5 28 20 20 20 21 11 102 48 48 15 5 5 28 20 20 20 20 20 20 20 20 20 20 20 20 20	Netan 83.6 84 93.3 80.5 98 98 56 95.5 83 98 83.6 84 93.3 80.5 98 56 56 95.5 83 80.5 83 98 56 56 56 95.5 83 98 56 96.5 83 96 56 98 56 83 98 56 98 56 83 98 83 6 98 80.6 84 93.3 80.5 56	sol sol 38.7 12 11.6 10.22 35 27 36 11 50); F = 6 11 50; F = 62 38.7 11.6 50 11.7 36.7 12.2 35.2 27.7 36.6 11 11.6 10.22 35.7 27.7 36.6 11 11.6 SD 38.7 12.1 11.6 10.22 11.2	112 24 15 28 20 34 18 11 242 7% Total 112 24 15 200 34 111 242 203 34 111 228 % 111 228 % Total 112 24 15 25 26 34 18 111 228 20 34 15 28 201 34 15 28	14.9% 17.6% 15.0% 19.9% 19.9% 19.9% 19.0% 19.9% 19.0% 19.0% 19.0% 19.0% 19.0% 19.0% 19.0% 19.0% 10	IV, Randolf, 200-Cl. 12.30 [2:18,09-Cl. -17.00 [2:4.30, -2.80] -17.00 [2:4.30, -2.80] -17.00 [2:4.30, -2.80] -17.00 [2:4.30, -2.80] -17.00 [2:4.30, -2.80] -16.40 [2:1.78, -11.01] -35.00 [2:6.44, -17.60] -19.16 [-25.19, -13.14] Mean Difference V, Random, 95% Cl -17.00 [2:4.30, -9.70] -17.00 [2:4.30, -9.70] -17.00 [2:4.30, -9.70] -35.00 [2:6.5, 4.35] -26.00 [3:4.40, -17.60] -13.00 [1:6.40, -21.70] -14.1022.30] -15.00 [1:8.40, -17.60] -16.40 [2:17, -11.01] -35.00 [2:6.5, 4.35] -26.00 [3:4.40, -17.60] -21.30 [2:1.80, -28.00] -21.30 [2:1.30, -21.30] -12.30 [2:1.30, -21.30] -13.10 [2:1.30, -21.30] -13.10 [2:1.30, -21.30] -13.10 [2:1.30, -21.30] -13.10 [2:1.30, -21.30] -13.10 [2:1.30, -21.30] -13.10 [2:1.30, -21.30] -13.10 [2:1.101]	N, Kandom, 95% Cl
Arevice 2019 di Lauro 2010 El-Batarry 2008 Faisal 2010 Hernandez Da Mota 2010 Manaba 2016 Motarres 2009 Rizzo 2008 Test for overall effect Z = 6: Study or Subgroup Arevice 2019 di Lauro 2010 El-Batarry 2008 Faisal 2018 Motarres 2009 Rizzo 2008 Total (65% CI) Heterogeneity, Tau* = 36.07 Total (o5% CI) Heterogeneity, Tau* = 36.07 Total (o5% CI) Heterogeneity, Tau* = 36.07 Total (o5% CI) Heterogeneity, Tau* = 36.07 Study or Subgroup Arevice 2019 di Lauro 2010 El-Batarry 2008 Faisal 2018 Heterogeneity, Tau* = 36.07 Total (o5% CI) Heterogeneity Tau* = 36.07 Study or Subgroup Arevice 2019 di Lauro 2010 El-Batarry 2008 Faisal 2018 Heterogeneity Tau* = 36.07 Study or Subgroup Arevice 2019 di Lauro 2010 El-Batarry 2008 Faisal 2018 Heterogeneity Arational effect Z = 7: Study or Subgroup	71.3 67 61.6 64.1 62 49 62 57 57 57 57 71.3 67 61.6 64.1 64.1 64.1 64.1 64.1 64.1 64.1	32.1 19.45 11.35 31 20 57.3 9 9 17.93, dt 10.00001) 9 e-op IVB 32.1 19.45 31 10.35 32.1 19.45 32.1 19.45 32.1 19.45 32.1 19.45 31 10.35 32.1 19.45 32.1 10.35 32.1 10	102 48 15 28 20 32 22 21 11 258 26 (P Total 102 48 15 28 20 32 22 21 11 258 8 26 6 (P Total 102 48 15 28 20 32 22 21 11 102 48 5 6 (P Total 102 5 8 20 20 22 22 21 11 102 5 8 20 20 22 22 21 11 102 5 8 20 20 22 22 21 11 102 5 8 20 20 22 22 21 11 102 5 8 20 20 22 22 21 11 102 5 8 20 20 22 22 21 11 102 5 8 20 20 22 22 22 11 102 5 8 20 20 22 22 22 21 11 102 5 8 20 20 22 22 22 21 11 102 5 8 20 20 22 22 22 22 22 22 22 22 22 22 22	Notation 83.6 83.6 83.6 83.6 83.6 98.8 56.5 83.3 80.5 98.8 80.5 98.8 80.5 83.8 80.5 83.8 80.5 83.8 66.9 95.5 83 80.5 83.8 56.6 98.8 56.6 95.5 83 95.5 83 96.5 98.3 80.5 98.8 86.4 94.3 83.6 84.4 93.3 80.5 98.8 86.5 98.8 86.5 98.8 80.5 98.8 86.5 98.8 80.5 98.8 80.5 98.8 80.5 98.8 80.5 98.8 80.5 98.8 80.5 98.8 80.5 98.8 80.5 98.8 8 80.5 98.8 <	sol 38.7 12. 11.6 35.7 27.36 11 30); P = 6 No IVB 38.7 12.2 13.6 11.6 10.22 36.7 12.11.6 11 10.22 36.7 37.7 11.6 10.22 38.7 12.11.6 10.22 38.7 12.11.6 10.22 38.7 12.11.6 10.22 38.7	112 24 155 28 20 34 18 11 242 27% Total 112 24 15 200 34 112 24 200 34 111 228 200 34 111 228 20 34 111 228 200 34 112 228 200 34 12 24 13 112 244 15 25 26 200 34 112 28 200 34 15 28 200 27	14.9% 17.6% 15.0% 19.9% 3.6% 3.6% 100.0% 12.8% 3.6% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.0%	IV, Ranzoni, Sob. 22, 801 -12, 30 (218, 30), 62, 801 -12, 30 (218, 30), 62, 801 -17, 00 (24, 30), 62, 701 -17, 01 (24, 30), 62, 701 -16, 40 (21, 78, -11, 011) -26, 00 (24, 40, -17, 601 -19, 16 (-25, 19, -13, 14] Mean Difference IV, Random, 95% (21, -13, 01, 62, 64, -15, 61) -13, 00 (26, 64, -15, 61) -13, 00 (26, 64, -16, 51) -10, 01 (24, 30), -200 -17, 00 (24, 30), -200 -17, 00 (24, 30), -200 -26, 00 (24, 42, 442) -26, 00 (26, 54, -35) -26, 00 (24, 42, 442) -26, 00 (24, 42, 442) -26, 00 (24, 42, 442) -26, 01 (24, 40, -17, 600) -26, 01 (24, 40, -17, 600) -26, 01 (24, 40, -17, 600) -21, 20 (21, 80, -200, -17, 600) -21, 20 (21, 80, -200, -17, 600) -12, 30 (23, 02, -17, 600) -13, 20 (21, 80, -200, -17, 600) -14, 10, 22, 300, -200, -200, -31, 700 (14, 10, -22, 300) -17, 700 (24, 20, -200, -200, -200) -17, 700 (24, 20, -200, -200) -17, 700 (24, 20, -200, -200) -17, 700 (24, 200, -200)	N, Kandom, 95% Cl
Arevaico 2019 - Arevaico 2019 - El-Batarry 2000 Faisal 2016 Hemrandez: Da Mota 2010 Manabe 2015 Modarres 2009 Ritzo 2008 Total (95% C) - Heterogeneily: Tau* = 39.89 - Test for overall effect: Z = 6. - Study or Subgroup - Arevalo 2019 - Gl.Lauro 2010 El-Batarry 2008 Total (95% CI) - Hetrogeneily: Tau* = 36.07 - Test for overall effect: Z = 7. - Study or Subgroup - Arevalo 2019 - di Lauro 2010 - El-Batarry 2008 - Total (95% CI) - Heterogeneily: Tau* = 36.07 - Test for overall effect: Z = 7. - Study or Subgroup - Arevalo 2019 - Hermandez: Da Mola 2010	71.3 67.3 67.6 64.1 62 49 62 49 62 57 7 1.3 7 7 1.3 67.6 64.1 62 2 9 9 2 2 (Prr Mean 7 1.3 67.6 64.1 62 2 12 (Pcr Prr Mean 62 7 7 1.5 6 7 6 7 6 7 6 7 6 7 6 7 6 7 6 7 6 7 7 7 7 7 7 8 7 7 7 7	32.1 19.45 10.35 31 20 57.3 9 9 17.93, dt 10.00001) 9 e-op IVB 50 32.1 19.45 14.5 31 10.35 32.1 19.45 14.5 31 10.35 57.3 9 9 15.97, dt 32.1 19.45 10.35 32.1 19.45 31 19.45 3119.45 31 19.45 19.45 19.45 19.45 19.45 19.45 19.45 19	102 48 15 28 20 32 22 21 11 258 8 26 (P Total 102 48 15 28 28 20 32 22 11 246 5 6 (P Total 102 48 15 28 20 32 22 21 11 10 24 5 8 20 20 22 21 11 10 25 8 20 20 22 21 11 10 25 8 20 20 22 21 21 11 10 25 8 20 20 22 21 21 11 10 25 8 20 20 22 21 21 11 10 25 8 20 20 22 21 21 11 10 25 8 20 20 22 21 21 11 10 25 8 20 20 22 21 11 10 25 8 20 20 22 21 21 11 10 25 8 20 20 20 21 21 11 10 25 8 20 20 21 11 10 25 20 20 20 20 20 20 20 20 20 20 20 20 20	mean 83.6 84 93.3 80.5 98 96.5 93 86 95.5 83 86 96.6 95.5 83 80.6 98 6 98 80.5 98 99.5 83 80.5 98.6 95.5 83 99.5 83 80.5 98.8 86 95.5 83.8 80.5 88 98.8 84 93.3 99.5 83 80.5 99.6 94.5 98 99.6 95.5 98	sol 38.7 12. 11.6 10.22 35 27 36 11 50): P = 6 SD 38.7 12.2 36.6 11 50: P = 62 37.7 11.6 10.22 36.7 11.6 11.7 38.7 12 11.6 10.22 38.7 12 11.0 38.7 12 11.0.22 36.7 12 13.6 10.22 36 10.22 35 27 36 10.22 36 27 36	112 24 15 28 20 34 18 11 242 7% 112 24 15 28 200 34 18 11 228 % Total 112 24 15 28 20 34 111 228 % Total 112 24 15 28 20 34 112 24 15 28 20 34 112 24 15 28 20 34 18	14,9%, 17,6%, 15,0%, 19,9%, 19,9%, 19,9%, 15,0%, 12,8%, 100,0%, 12,8%, 100,0%, 100,0%, 16,9%, 16,9%, 14,7%, 19,0%, 12,8%, 12,8%, 100,0%, 14,9%, 12,8%, 12,8%, 12,8%, 12,8%, 12,8%, 12,8%, 12,8%, 12,8%, 12,8%, 12,8%, 12,8%, 12,9%, 12,9%, 12,9%, 12,9%, 14,9%,14,9%, 14,9%, 14,9%,14,9%, 14,9%,14,9%, 14,9%,14,9%,14,9%, 14,9%,14,9%,14,9%,14,9%	IV, Randoni, 30%-CI. 12.30 (2140) 12.30 (2140) 14.20 (2140) 14.20 (2140) 14.20 (2140) 14.20 (2140) 15.20	N, Kandom, 95% Cl
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Arevalo 2019 Arevalo 2019 E-Batamy 2008 Faisal 2019 Faisal 2018 Hermandez:Do a Mota 2010 Manabe 2015 Modarres 2009 Total (95% CI) Heterogenetik, Tau* = 39.89 Test for overall effect 2 = 6: Study or Subgroup Arevalo 2019 di Lauro 2010 E-Batamy 2008 Total (95% CI) Heterogenetik, Tau* = 36.07 Test for overall effect 2 = 7: Study or Subgroup Arevalo 2019 di Lauro 2010 E-Batamy 2008 Total (95% CI) Heterogenetik, Tau* = 36.07 Test for overall effect 2 = 7: Study or Subgroup Arevalo 2019 di Lauro 2010 E-Batamy 2008 Total (95% CI) Hotal (95% CI)	71.3 67 61.6 64.1 62 49 62 57 7 81.6 67 71.3 67 61.6 64.1 62 57 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.6 84.1 64.1 64.1 64.1 64.1 64.1 64.1 64.1 6	32.1 19.45 14.5 10.35 31 20 57.3 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	102 48 55 28 20 32 22 11 258 56 (P 7 7 0 102 48 55 6 (P 7 7 0 102 48 20 22 21 11 246 56 (P 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	mean 83.6 84 83.6 84 85 98 56 95.5 83 98 56 96.5 83 83.6 84 93.3 80.5 98 56 95.5 98 98 56 95.5 98 99.5 98 80.6 99.5 99.6 93.3 80.5 84 93.3 80.5 83 98 98 96 84 93.3 99.5 83 98 96 99.5 83 98 95.5 93	sub 38.7 12.387 11.6 10.22 35 27 36 11 50; F = 6 No IVB SB.7 12 11.6 10.22 38.7 12 11.6 10.22 36 11 10.22 38.7 12 11.6 10.22 35 27 36 11 12 12 13.6 10.22 35 27 36 11 10.22 35 27 36 11.1	1112 24 115 28 200 34 18 11 242 27% Total 112 24 15 28 20 34 18 111 244 15 28 20 34 111 228 % Total 112 24 15 28 20 34 111 228 % Total 112 244 244 244	14.9% 17.8% 17.8% 19.9% 19.9% 19.9% 19.9% 19.0% 19.9% 10.0% Weight 10.0% Weight 10.0% Weight 10.0% Weight 14.8% 10.0% Weight 14.7% 6.5% 10.0% 10.5% 10.5% 10.0% 10.5% 10.0% 10.5% 10.0% 10.0% 10.5%	IV, Raitoni, Sov. 2.80; 12.30 [:21.80], C.2.80; -17.00 [:24.30, -2.70]; -31.70 [:41.10, -22.30]; -16.40 [:21.78, -11.01]; -35.00 [:56.44, -15.51]; -30.00 [:56.44, -17.60]; -19.16 [:25.19, -13.14]; Mean Difference VK, Random, 95% C1 -12.30 [:21.80, -28.01]; -12.30 [:21.80, -28.01]; -12.30 [:21.80, -28.01]; -12.30 [:21.80, -28.01]; -12.30 [:21.80, -28.01]; -12.30 [:21.80, -28.01]; -12.30 [:21.80, -28.01]; -12.30 [:22.80, -28.01]; -12.30 [:24.30, -8.70]; -12.30 [:24.30, -8.70]; -12.30 [:24.30, -2.80]; -12.30 [:24.30, -2.80]; -12.30 [:24.30, -2.80]; -12.30 [:24.30, -2.80]; -12.30 [:24.30, -2.80]; -12.30 [:24.30, -2.80]; -12.30 [:26.01, -24.30, -7.70]; -13.17 [:41.10, -22.30]; -13.07 [:24.30, -2.80]; -14.41 [:24.30]; -12.30 [:26.30, -2.80]; -13.17 [:41.10]; -26.00 [:34.41, -17.60]; -27.20 [:24.30, -2.80];	N, Kandom, 95% Cl
Arevia 2019 Arevia 2019 di Lauro 2010 El-Batarry 2008 Hernandez Da Mola 2010 Manabe 2018 Motarres 2009 Rizzo 2008 Toda (05% C) Heterogenety, Tau* = 38.09 Rizzo 2008 Toda (05% C) Heterogenety, Tau* = 36.07 Rest for overall effect Z = 6.1 Study or Subgroup Arevia 2019 Rizzo 2008 Rizzo 2008 Toda (05% C) Heterogenety, Tau* = 36.07 Test for overall effect Z = 7.1 Study or Subgroup Arevia 2019 Rizzo 2008 Toda (05% C) Heterogenety, Tau* = 36.07 Test for overall effect Z = 7.1 Study or Subgroup Arevia 2019 Hernandez:Da Mola 2010 Bisala 2018 Hernandez:Da Mola 2010 Bisala 2018 Hernandez:Da Mola 2010 Rizzo 2008 Toda (05% C) Heterogenety, Tau* = 44.87 Heterogenety, Tau	71.3 67 61.6 64.1 62 49 62 57 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.3 67 71.5 64.1 64.1 64.1 64.1 64.1 64.1 64.1 64.1	32.1 19.45 11.35 11.45 11.35 11.35 11.35 19 30.00001) 30.00001) 30.00001) 30.00001) 30.00001) 30.1 19.45 10.35 30.1 19.45 30.1	Total 102 48 15 28 20 21 102 48 101 258 20 1102 48 15 28 202 11 2466 7 102 48 15 282 211 2466 7 7 248 202 1102 48 105 28 202 11 246 6 7 2102 1102 48 105 28 202 211 256 56	mean 83.6 84 83.6 84 85 98.8 56 95.5 83 98.8 84 93.3 80.5 83.6 84 93.3 80.5 98.8 56 95.5 98 99.5 98 98 98 99.6 93.3 80.5 84 93.3 80.5 83 84 93.3 80.5 83 84 93.3 80.5 83 86 98 84 93.3 80.5 83 98 56 83 95.5 83 99 83.5 83 95.5 83	sol sol 38.7 12 11.6 10.22 35 7 36.7 12 35 7 36 11 37 36 38.7 12 38.7 12 38.7 12 38.7 10.22 35 77 36 10.22 38.7 11.6 10.22 35 277 36 38.7 12 11.6 10.22 38.7 12 38.7 12 38.7 12 36.7 12 36.7 36 30; I*= 6 30; I*= 6	Total 112 24 15 28 200 34 18 112 242 27% Total 112 24 15 28 20 34 111 228 % Total 112 228 % Total 112 244 9%	14.9% 17.6% 17.6% 15.0% 19.9% 19.9% 10.0% 10.0% Weight 15.9% 16.0% 0.0% 16.2% 100.0% Weight 14.6% 14.6% 14.6% 15.7% 100.0%	IV, Randolf, 307-621 12.30 [2:10, 2-260] -17.00 [2:4.30, -270] -31.70 [4:11, 0:22.30] -16.40 [2:1.79, -11.01] -70.00 [18.42, 14.2] -35.50 [2:65, 4.35] -26.00 [-34.40, -17.60] -19.16 [-25.19, -13.14] Mean Difference VK, Random, 95% C1 -17.00 [2:43.00, -870] -31.70 [-41.10, -22.30] -32.50 [-26.56, -4.35] -26.00 [-34.40, -17.60] -17.00 [-43.00, -970] -31.70 [-41.01, -22.30] -30.50 [-56.42, 4.2] -32.50 [-26.56, -4.35] -26.00 [-34.40, -17.60] -31.70 [-41.02, -2800] -30.50 [-52.46, -4.55] -26.00 [-54.40, -17.60] -21.38 [-27.91, -15.86] Mean Difference VK, Random, 95% C1 -17.00 [-24.30, -9.70] -13.70 [-41.00, -28.0] -14.00 [-56.49, -15.51] -13.70 [-41.01, -22.30] -16.40 [-21.79, -11.01] -36.00 [-56.44, -15.51] -30.01 [-56.42, -13.55] -26.00 [-54.40, -17.60] -26.00 [-54.40, -17.60]	N, Kandom, 95% Cl
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Arevaico 2019 Arevaico 2019 Lauro 2010 El-Batarry 2008 Faisal 2016 Modares 2016 Modares 2009 Rizz 2008 Total (95% CI) Heterogeneily, Tau* = 39.89 Test for overall effect. Z = 6. Study or Subgroup Arevalo 2019 Al Lauro 2010 El-Batarry 2008 Total (95% CI) Heterogeneily, Tau* = 36.07 Test or overall effect. Z = 7. Study or Subgroup Arevalo 2019 di Lauro 2010 El-Batarry 2008 Total (95% CI) Heterogeneily, Tau* = 36.07 Test for overall effect. Z = 7. Study or Subgroup Arevalo 2019 di Lauro 2010 Faisal 2018 Hermandez-Da Mola 2010 Modares 2009 Rizzo 2008 Total (95% CI) Heterogeneik, Tau* = 44.87 Test for overall effect. Z = 4.27 Test for overall effect. Z = 6. Study or Subgroup	71.3 67.3 67.6 64.1 62.4 49 62.2 57 71.3 67.6 64.1 62.4 49 62.2 57 71.3 67.6 64.1 62.4 49 62.2 57 71.3 67.6 64.1 62.4 96.2 57 71.3 67.6 64.1 62.2 49.9 62.2 57 71.3 67.6 64.1 62.4 96.2 57 71.3 67.6 64.1 62.4 96.2 57 71.3 67.6 64.1 62.4 96.2 57 71.3 67.6 64.1 62.4 96.2 57 71.3 67.6 64.1 62.4 96.2 57 71.3 67.6 64.1 62.4 96.2 57 71.3 67.6 64.1 62.5 71.3 67.6 64.1 62.5 71.3 67.6 64.1 62.5 71.3 67.6 64.1 62.5 75.5 71.3 67.6 64.1 64.1 62.5 75.	32.1 32.1 19.45 31 14.5 31 20 57.3 9 9 17.93, dt 10.00001) sop IVB 50 32.1 19.45 31 19.45 31 10.35 32.1 19.45 31 19.45 19.4	102 102 48 15 15 28 20 32 22 11 258 8 20 32 22 11 102 48 15 28 20 32 22 11 102 48 15 28 20 22 21 11 258 8 20 20 22 21 11 258 20 20 22 21 11 258 20 20 22 22 11 258 20 20 22 22 11 258 20 20 22 22 11 246 6 (P Total 102 248 20 22 22 11 258 28 20 22 22 11 246 6 (P Total 102 248 20 22 22 11 246 28 20 22 22 11 246 6 (P Total 102 248 20 22 22 21 11 246 6 (P Total 102 248 20 22 22 11 246 6 (P Total 102 248 20 22 22 11 246 6 (P Total 28 20 22 22 11 246 6 (P Total 28 20 22 22 11 246 6 (P Total 28 20 22 22 11 246 6 (P Total 28 20 22 22 11 246 6 (P Total 28 20 22 22 11 246 6 (P Total 28 20 22 22 11 256 (P Total 102 22 22 11 256 (P Total Total 102 22 22 11 256 (P Total 10 256 (P Total 10 256 (P Total 10 256 (P Total 10 256 (P Total 10 10 10 10 10 10 10 10 10 10	Interim 83.6 84 84 93.3 80.5 98 98 56 98 95.5 83 93.3 80.5 98 83.6 84 93.3 80.5 83 80.5 83 80.5 83 80.5 83 83.6 84 93.3 80.5 83 85.6 83.4 96.5 83 85.5 83 85.5 83 96.5	sol sol 38.7 12 31.7 12 31.7 12 31.7 36.7 31.7 36.7 31.7 12 31.7 12 31.7 12 31.7 12 31.7 12 31.7 12 31.7 36 11.1 10.22 35 27 36 10.22 35 11.1 31.7 12 11.1 10.22 35 17.6 30.7 12 31.1 11.1 31.1 11.1 31.1 11.1 31.1 11.1	1112 24 112 24 200 34 118 7% Total 112 244 18 112 24 200 34 1112 244 200 34 1112 248 200 34 1112 248 200 34 1112 244 9% Total	14.9% 17.8% 17.8% 17.8% 19.9% 19.9% 19.9% 19.9% 19.9% 10.0% 12.8% 10.0% Weight 15.9% 16.0% 0.0% 15.9% 16.0% 0.0% 16.2% 100.0% Weight 100.0% Weight 100.0% Weight 100.0% Weight 100.0% Weight 100.0% Weight 100.0% Weight 100.0% 10.5% 100.0% 10.5% 10.0% 10.5% 10.0% 10.5% 10.0% 10.5% 10.0% 10.5% 10.0% 10.0% 10.5% 10.0% 1	IV, Randon, Sob. Cl. 12.30 (214) 12.30 (214) 13.70 (4-1), 0-22.30) 14.70 (4-1), 0-22.30) 15.70 (4-1), 0-22.30) 16.40 (21.78, -11.01) -7.00 (-18.42, 4.42) -3.50 (-26.56, -4.36) -3.50 (-26.56, -4.36) -26.00 (-34.40, -17.60) -19.16 (-25.19, -13.14) Mean Difference W, Random, 95% C1 -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -26.00 (-34.40, -17.60) -26.00 (-34.40, -17.60) -26.00 (-34.40, -17.60) -28.00 (-34.40, -17.60) -28.00 (-34.40, -17.60) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70)	N, Kandom, 95% Cl
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16.9% 16.9% 15.9% 16.9% 16.9% 16.9% 16.9% 16.9% 16.9% 17.4% 10.0% 19.9% 19.2% 19.2% 19.2% 19.2% 10.0%	IV, Rattorit, 307-621 12.30 (214) 12.30 (214) 13.70 (4-11, 0-22.30) 14.70 (4-11, 0-22.30) 15.70 (4-11, 0-22.30) 16.40 (21.78, -11.01) -7.00 (-18.42, 4.42) -3.50 (-25.64, -15.51) -7.50 (-18.44, -17.60) -19.16 (-25.19, -13.14) Mean Difference W, Random, 95% (1 -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -17.00 (-24.30, -9.70) -3.170 (-41.10, -22.30) -3.00 (-56.42, -14.51) -26.00 (-34.40, -17.60) -26.00 (-54.42, 4.42) -3.50 (-56.55, -4.35) -26.00 (-34.40, -17.60) -28.00 (-34.40, -17.60) -12.30 (-21.80, -2.80) -17.00 (-24.30, -8.70) -17.00 (-24.30, -8.70) -16.40 (-21.79, -11.01) -3.50 (-56.55, -4.35) -26.00 (-34.40, -17.60) -17.00 (-18.42, 4.42) -3.50 (-56.55, -4.35) -26.00 (-34.40, -17.60) -17.00 (-18.42, 4.42) -3.50 (-56.55, -4.35) -26.00 (-34.0, -17.60) <t< td=""><td>N, Kandom, 95% Cl</td></t<>	N, Kandom, 95% Cl
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Arevia 2019 Arevia 2019 4 Lauro 2010 El-Batarry 2008 Hemandez Da Mola 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% C) Heterogeneity, Tau" = 38.89 Test for overall effect Z = 6. Study or Subgroup Arevia 2019 El-Batarry 2008 Faisal 2018 Hemandez Da Mola 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% C) Heterogeneity, Tau" = 38.07 Test for overall effect Z = 7. Study or Subgroup Arevia 2018 Hemandez Da Mola 2010 Manabe 2015 Modarres 2009 Rizzo 2008 Total (95% C) Heterogeneity, Tau" = 48.07 Meratory 2018 El-Batarry 2008 Total (95% C) Heterogeneity, Tau" = 44.87 Test for overall effect Z = 6. Study or Subgroup Arevia 2019 di Lauro 2010 El-Batarry 2008 Total (95% C) Heterogeneity, Tau" = 44.87 Test for overall effect Z = 6. 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9 9 19,45 10,35 19,45 19,45 19,45 19,45 19,45 19,45 19,45 10,57,3 19,45 10,57,3 11,57,3 11,57,4 11,57,4 11,57,45 17,57,45 1	Total 102 48 48 5 28 22 11 258 28 22 11 102 48 32 222 11 102 48 200 32 211 246 102 48 102 48 102 48 200 32 2211 256 102 48 15 28 200 32 211 256 26 (P 102 48 102 48 102 211 256 22 11 258 20 32 211 256 22 211 256 6 211 25 22 21 100 32 22 <td>mean 83.6 83.8 93.3 83.6 93.3 80.5 98 56 83 98.3 83.6 83.6 84 93.3 98 83.6 84 93.3 83.6 98 86 95.5 83 = 0.011) 10 1 10 1 83.6 98 56 98 56 98 56 98 56 98 56 98 56 98 56 99.5 83 98 56 98 56 93.3 80.5 98 56 93.3 80.5 98 56 98 56 83 80.5 98 56 98 56 98 56</td> <td>stop 38.7 38.7 11.6 10.22 35.7 12.35 276 36.7 38.7 10.22 38.7 11.6 30.7 11.6 30.7 12 11.6 10.22 38.7 12 11.6 10.22 38.7 12 11.6 10.22 38.7 11.2 11.2 38.7 12 13.8 11.1 (P=6 SD 38.7 11.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 13.1 <td>Total 112 24 112 24 24 34 112 24 27% 7% Total 112 24 24 112 24 24 34 111 242 24 34 111 228 % 112 244 15 28 20 34 11 244 15 28 20 34 11 244 15 28 20 34 11 244 18 111 244 12 24 14 15 28 20 34 18 111 251 28 11 251 16%</td><td>14.9% 17.6% 17.6% 17.6% 17.6% 19.9% 19.9% 19.9% 12.8% 28.5% 16.2% 16.2% 16.2% 16.0% 21.7% 16.0% 21.7% 14.6% 0.0% 100.0% Weight 14.6% 0.0% 100.0% 100.0%</td><td>IV, Rattorit, 307-621 12.30 (2-18, 307-62) -17.00 (2-4.30, -8.70) -17.00 (2-4.30, -8.70) -31.70 (2-4.10, -22.30) -16.40 (2-1.78, -11.01) -35.60 (2-56.44, -12.50) -35.60 (2-56.43) -35.60 (2-56.43) -26.00 (2-44.0, -17.60) -19.16 (2-55.9, -13.14) Mean Difference VK, Random, 95% C1 -12.30 (2-18.00, -2.80) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -26.00 (3-44.0, -17.60) -27.30 (1-62.65, -4.35) -28.00 (3-44.0, -17.60) -12.30 (2-18.0, -2.80) -12.30 (2-18.0, -2.80) -13.70 (1-64.2, 4.24) -35.0 (1-62.65, -4.35) -26.00 (3-44.0, -17.60) -17.00 (1-64.20, -8.70) -17.00 (1-64.20, -8.70) -17.00 (1-64.20, -8.70) -17.00 (1-76.42, 4.42) -35.0 (1-62.65, -4.35) -17.00 (1-76.42, -4.72) -17.00 (1-76.42, -4.72)</td><td>N, Kandom, 95% CI</td></td>	mean 83.6 83.8 93.3 83.6 93.3 80.5 98 56 83 98.3 83.6 83.6 84 93.3 98 83.6 84 93.3 83.6 98 86 95.5 83 = 0.011) 10 1 10 1 83.6 98 56 98 56 98 56 98 56 98 56 98 56 98 56 99.5 83 98 56 98 56 93.3 80.5 98 56 93.3 80.5 98 56 98 56 83 80.5 98 56 98 56 98 56	stop 38.7 38.7 11.6 10.22 35.7 12.35 276 36.7 38.7 10.22 38.7 11.6 30.7 11.6 30.7 12 11.6 10.22 38.7 12 11.6 10.22 38.7 12 11.6 10.22 38.7 11.2 11.2 38.7 12 13.8 11.1 (P=6 SD 38.7 11.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 12.2 38.7 13.1 <td>Total 112 24 112 24 24 34 112 24 27% 7% Total 112 24 24 112 24 24 34 111 242 24 34 111 228 % 112 244 15 28 20 34 11 244 15 28 20 34 11 244 15 28 20 34 11 244 18 111 244 12 24 14 15 28 20 34 18 111 251 28 11 251 16%</td> <td>14.9% 17.6% 17.6% 17.6% 17.6% 19.9% 19.9% 19.9% 12.8% 28.5% 16.2% 16.2% 16.2% 16.0% 21.7% 16.0% 21.7% 14.6% 0.0% 100.0% Weight 14.6% 0.0% 100.0% 100.0%</td> <td>IV, Rattorit, 307-621 12.30 (2-18, 307-62) -17.00 (2-4.30, -8.70) -17.00 (2-4.30, -8.70) -31.70 (2-4.10, -22.30) -16.40 (2-1.78, -11.01) -35.60 (2-56.44, -12.50) -35.60 (2-56.43) -35.60 (2-56.43) -26.00 (2-44.0, -17.60) -19.16 (2-55.9, -13.14) Mean Difference VK, Random, 95% C1 -12.30 (2-18.00, -2.80) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -26.00 (3-44.0, -17.60) -27.30 (1-62.65, -4.35) -28.00 (3-44.0, -17.60) -12.30 (2-18.0, -2.80) -12.30 (2-18.0, -2.80) -13.70 (1-64.2, 4.24) -35.0 (1-62.65, -4.35) -26.00 (3-44.0, -17.60) -17.00 (1-64.20, -8.70) -17.00 (1-64.20, -8.70) -17.00 (1-64.20, -8.70) -17.00 (1-76.42, 4.42) -35.0 (1-62.65, -4.35) -17.00 (1-76.42, -4.72) -17.00 (1-76.42, -4.72)</td> <td>N, Kandom, 95% CI</td>	Total 112 24 112 24 24 34 112 24 27% 7% Total 112 24 24 112 24 24 34 111 242 24 34 111 228 % 112 244 15 28 20 34 11 244 15 28 20 34 11 244 15 28 20 34 11 244 18 111 244 12 24 14 15 28 20 34 18 111 251 28 11 251 16%	14.9% 17.6% 17.6% 17.6% 17.6% 19.9% 19.9% 19.9% 12.8% 28.5% 16.2% 16.2% 16.2% 16.0% 21.7% 16.0% 21.7% 14.6% 0.0% 100.0% Weight 14.6% 0.0% 100.0% 100.0%	IV, Rattorit, 307-621 12.30 (2-18, 307-62) -17.00 (2-4.30, -8.70) -17.00 (2-4.30, -8.70) -31.70 (2-4.10, -22.30) -16.40 (2-1.78, -11.01) -35.60 (2-56.44, -12.50) -35.60 (2-56.43) -35.60 (2-56.43) -26.00 (2-44.0, -17.60) -19.16 (2-55.9, -13.14) Mean Difference VK, Random, 95% C1 -12.30 (2-18.00, -2.80) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -17.00 (2-43.0, -8.70) -26.00 (3-44.0, -17.60) -27.30 (1-62.65, -4.35) -28.00 (3-44.0, -17.60) -12.30 (2-18.0, -2.80) -12.30 (2-18.0, -2.80) -13.70 (1-64.2, 4.24) -35.0 (1-62.65, -4.35) -26.00 (3-44.0, -17.60) -17.00 (1-64.20, -8.70) -17.00 (1-64.20, -8.70) -17.00 (1-64.20, -8.70) -17.00 (1-76.42, 4.42) -35.0 (1-62.65, -4.35) -17.00 (1-76.42, -4.72) -17.00 (1-76.42, -4.72)	N, Kandom, 95% CI

Figure 15. Sensitivity analyses of preoperative IVB effect on operation time according to the leave-one-out method.

When controlling for different doses by excluding the two studies that used IVB concentration different than the standard 1.25 mg/0.05 mL, all comparisons remained statistically significant (Figures 20–24).

Publication bias

Publication bias was assessed by using funnel plots for each separate comparison. All plots were symmetrical, except for operation time. The asymmetry may be due to differences in surgeons' skills, surgical equipment among studies and complexity of cases (Figures 25–29).

Discussion

Advanced PDR treatment remains a surgical challenge, especially in cases of TRD. Uncontrolled intraoperative bleeding increases surgical time and may lead to intraoperative complications such as iatrogenic retinal breaks due to impaired retina view. Segmentation and delamination of fibrovascular membranes are complex steps, with increased risk or retinal tears or intraoperative bleeding.⁹ Improving outcomes in such challenging cases is important, particularly because they frequently involve patients of working age, with all the social an economic consequences that entails.⁵²

The first documented use of preoperative IVB in diabetic vitrectomy was by Chen et al. who administered a single IVB in a 27-year-old patient reporting promising results.⁵³ Since then, many studies have been conducted on the efficacy of preoperative IVB in patients undergoing diabetic vitrectomy. Since then, a large number of publications have also suggested its clinical utility, and the benefits of preoperative IVB have been also demonstrated at molecular level.^{47,49}

The present systematic review aimed to provide an up to date assessment of the use of preoperative IVB as an adjunct to diabetic vitrectomy. Our results found that a single preoperative dose of IVB was associated with a shorter mean surgical time and less iatrogenic retinal breaks. Moreover, patients pretreated with IVB were shown to have statistically significantly better BCVA on last follow-up visit, fewer episodes of POVCH and a reduced revision vitrectomy rate.

Regarding the mean operation time, evidence from 8 studies was pooled. Except for the study of



Figure 16. Sensitivity analyses of preoperative IVB effect on iatrogenic intraoperative retinal breaks occurrence according to the leave-one-out method.



Figure 17. Sensitivity analyses of preoperative IVB effect on best-corrected visual acuity at the last follow-up visit.

Study or Subgroup	Pre-op Events	IVB Total	No IVI Events	3 Total	Weight	Odds Ratio M-H. Random, 95% Cl	Odds Ratio M-H. Random, 95% Cl	
Ahmadieh 2009 Ahn 2011	9	35	26	33 34	0.0%	0.09 [0.03, 0.29]		
Arevalo 2019 di Lauro 2010	29 3	102 48	48	112	26.3%	0.53 [0.30, 0.94] 0.20 [0.05, 0.89]		
El-Batarny 2008 Hernandez-Da Mota 2010	0	15 20	4	15 20	4.2% 13.1%	0.08 [0.00, 1.69] 0.38 [0.09, 1.54]		
Manabe 2015 Modarres 2009	1 0	32 22	8 7	34 18	7.4% 4.4%	0.10 [0.01, 0.89] 0.03 [0.00, 0.65]		
Zaman 2013	3	24	20	30	13.0%	0.07 [0.02, 0.30]		
Total (95% CI) Total events	53	299	119	287	100.0%	0.25 [0.13, 0.48]	-	
Heterogeneity: Tau* = 0.35; Test for overall effect: Z = 4.	Chi*=12.) 11 (P < 0.0	50, df = 1001)	7 (P = 0.0	18); I*=	: 44%		0.005 0.1 1 10 Favours [Pre-op IVB] Favours [No IVB]	200
Study or Subgroup	Pre-op Events	IVB Total	No IVI Events	3 Total	Weight	Odds Ratio	Odds Ratio	
Ahmadieh 2009	9	35	26	33	16.8%	0.09 [0.03, 0.29]		
Arevalo 2019 di Lauro 2010	29	102	48	112	22.8%	0.53 [0.30, 0.94]		
El-Batarny 2008 Hernandez-Da Mota 2010	0	15 20	4 8	15 20	5.2% 13.9%	0.08 [0.00, 1.69] 0.38 [0.09, 1.54]		
Manabe 2015 Modarres 2009	1	32 22	8 7	34 18	8.7% 5.4%	0.10 [0.01, 0.89] 0.03 [0.00, 0.65]	·	
Zaman 2013	3	24	20	30	13.8%	0.07 [0.02, 0.30]		
Total (95% CI) Total events	49	298	127	286	100.0%	0.17 [0.08, 0.37]	•	
Heterogeneity: Tau ² = 0.60; Test for overall effect: Z = 4.	Chi ² = 15. 48 (P < 0.0	85, df= 10001)	7 (P = 0.0)3); I*=	: 56%		0.005 0.1 10 Favours [Pre-op IVB] Favours [No IVB]	200
Study or Subgroup	Pre-op	NB Total	No IVI	B Total	Weight	Odds Ratio	Odds Ratio	
Ahmadieh 2009	9 12	35	26	33	19.0%	0.09 [0.03, 0.29]		
Arevalo 2019 di Lauro 2010	29	102	48	112	0.0%	0.53 [0.30, 0.94]		
El-Batarny 2008	0	15	4	15	4.3%	0.08 [0.00, 1.69]		
Manabe 2015 Modarres 2009	1	32	8	34	7.8%	0.10 [0.01, 0.89]		
Zaman 2013	3	24	20	30	14.2%	0.07 [0.02, 0.30]		
Total (95% CI) Total events	33	232	97	208	100.0%	0.17 [0.09, 0.33]	•	
Heterogeneity: Tau ^a = 0.27; Test for overall effect: Z = 5.	Chi ² = 10. 26 (P < 0.0	16, df= 10001)	7 (P = 0.1	18); I*=	31%		0.005 0.1 1 10 Favours IPre-op IVRI Favours INo IVRI	200
Charles Cal	Pre-op	NB	No IVI	3		Odds Ratio	Odds Ratio	
Ahmadieh 2009	Events 9	1otal 35	Events 26	10tal 33	vveight 16.0%	nn-H, Kandom, 95% Cl 0.09 [0.03, 0.29]	M-H, Random, 95% Cl	
Ahn 2011 Arevalo 2019	13 29	36 102	18	34 112	17.8%	0.50 (0.19, 1.31) 0.53 (0.30, 0.94)	-	
di Lauro 2010 El-Batarny 2008	3	48	6	24	0.0% 4.9%	0.20 [0.05, 0.89] 0.08 [0.00, 1.69]		
Hernandez-Da Mota 2010 Manabe 2015	4	20 32	8	20 34	13.2% 8.1%	0.38 [0.09, 1.54] 0.10 [0.01, 0.89]		
Modarres 2009 Zaman 2013	0	22 24	7 20	18 30	5.1% 13.1%	0.03 [0.00, 0.65] 0.07 [0.02, 0.30]		
Total (95% CI)	50	286	420	296	100.0%	0.20 [0.10, 0.43]	•	
Heterogeneity: Tau ² = 0.57; Test for controll offect: 7 = 4	Chi ² = 16.9	92, df=	7 (P = 0.0	02); I*=	59%		0.005 0.1 1 10	200
resciol oferall ellect 2 = 4.	Pre-op	IVB	No IVI	3		Odds Ratio	Favours (Pre-op IVB) Favours (No IVB) Odds Ratio	
Study or Subgroup Ahmadieh 2009	Events 9	Total 35	Events 26	Total 33	Weight 14.9%	M-H, Random, 95% Cl 0.09 [0.03, 0.29]	M-H, Random, 95% Cl	
Ahn 2011 Arevalo 2019	13 29	36 102	18 48	34 112	16.7% 21.1%	0.50 [0.19, 1.31] 0.53 [0.30, 0.94]		
di Lauro 2010 El-Batarny 2008	3	48 15	6	24 15	11.5%	0.20 [0.05, 0.89] 0.08 [0.00, 1.69]		
Hernandez-Da Mota 2010 Manabe 2015	4	20 32	8	20	12.1%	0.38 [0.09, 1.54] 0.10 [0.01, 0.89]		
Modarres 2009 Zaman 2013	0 3	22 24	7 20	18 30	4.5% 12.0%	0.03 [0.00, 0.65] 0.07 [0.02, 0.30]	·	
Modarres 2009 Zaman 2013 Total (95% CI)	0 3	22 24 319	7 20	18 30 305	4.5% 12.0% 100.0%	0.03 (0.00, 0.65) 0.07 (0.02, 0.30) 0.22 (0.11, 0.43)	←	
Modarres 2009 Zaman 2013 Total (95% CI) Total events Heterogeneity: Tau ² = 0.50;	0 3 62 Chi ² = 16.	22 24 319 46, df=	7 20 141 7 (P = 0.0	18 30 305 (2); I ² =	4.5% 12.0% 100.0%	0.03 (0.00, 0.65) 0.07 (0.02, 0.30) 0.22 (0.11, 0.43)		200
Modarres 2009 Zaman 2013 Total (95% CI) Total events Heterogeneith: Tau ² = 0.50; Test for overall effect: Z = 4.	0 3 62 Chi ² = 16. 38 (P < 0.0	22 24 319 46, df = 1001)	7 20 141 7 (P = 0.0	18 30 305 02); P=	4.5% 12.0% 100.0%	0.03 (0.00, 0.65) 0.07 (0.02, 0.30) 0.22 (0.11, 0.43)	0.005 0.1 10 Favours [Pre-op IVB] Favours [No IVB]	200
Modarres 2009 Zaman 2013 Total (95% CI) Total events Heterogeneity: Tau ² = 0.50; Test for overall effect: Z = 4. Study or Subgroup Abmadich 2009	0 3 62 Chi ² = 16. 38 (P < 0.0 Pre-op Events	22 24 319 46, df = 1001) IVB Total	7 20 141 7 (P = 0.0 No IVI Events 26	18 30 305)2); I ² = 3 <u>Total</u> 22	4.5% 12.0% 100.0% 57% Weight	0.03 [0.00, 0.65] 0.07 [0.02, 0.30] 0.22 [0.11, 0.43] Odds Ratio M-H, Randorn, 95% CI	0005 0.1 10 Favours (Pre-op IVB) Favours (No IVB) Odds Ratio M.H. Random, 95% CI	200
Modarres 2009 Zaman 2013 Total (95% CI) Total events Heterogeneity: Tau ² = 0.50; Test for overall effect: Z = 4. <u>Study or Subgroup</u> Ahmadien 2009 Ahm 2011 Accesing 2019	0 3 Chi ² = 16. 38 (P < 0.0 <u>Pre-op</u> <u>Events</u> 9 13 29	22 24 319 46, df = 1001) IVB Total 35 36 102	7 20 141 7 (P = 0.0 <u>No IVI</u> <u>Events</u> 26 18	18 30 305 02); F= 3 <u>Total</u> 33 34 112	4.5% 12.0% 100.0% 57% Weight 16.0% 17.8% 21.9%	0.03 (0.00, 0.65) 0.07 (0.02, 0.30) 0.22 (0.11, 0.43) 0.04ds Ratio M-H, Random, 95% CI 0.09 (0.03, 0.29) 0.50 (0.19, 1.31) 0.50 (0.19, 1.31)	0.005 0.1 Favours No MBJ Pavours (Pre-op //B) Favours No MBJ 0.0046 Ratio MH, Random, 95% Cl	200
Modarres 2009 Zaman 2013 Total (95% CI) Total events Heterogeneity: Tau*e 0.50; Test for overall effect Z = 4. <u>Study or Subgroup</u> Ahmadien 2009 Ahm 2011 Arevalo 2019 di Lauro 2010 di Lauro 2010	0 3 Chi ² = 16. 38 (P < 0.0 Pre-op Events 9 13 29 3 0	22 24 319 46, df = 1001) IVB Total 35 36 102 48 15	7 20 141 7 (P = 0.0 No IVI Events 26 18 48 6 48 6	18 30 305 02); F= 3 Total 33 34 112 24 15	4.5% 12.0% 100.0% 57% Weight 16.0% 17.8% 21.9% 12.6%	0.03 (0.00, 0.65) 0.07 (0.02, 0.30) 0.22 (0.11, 0.43) 0.05 (0.11, 0.43) 0.09 (0.03, 0.29) 0.50 (0.19, 1.31) 0.53 (0.30, 0.94) 0.53 (0.30, 0.94) 0.53 (0.30, 0.94) 0.53 (0.30, 0.94)	0005 01 10 Favours (Pic-top /KB) Favours (Pic-top /KB) Odds Ratio MH, Random, 95% Cl	200
Modarres 2009 Zaman 2013 Total (95% C) Total revents Heterogeneik; Tau? = 0.50; Test for overall effect Z = 4. <u>Study or Subgroup</u> Ahmaden 2009 Ahm 2011 Arenalo 2019 di Lauro 2010 Heteromatez Da Mota 2010 Menahe 2015	0 3 62 Chi ^p = 16. 38 (P < 0.0 Pre-op Events 9 13 299 3 0 4 1	22 24 319 46, df = 1001) IVB Total 35 36 102 48 15 20 32	7 20 141 7 (P = 0.0 <u>No IVI</u> 26 18 48 48 6 4 8 8	34 18 30 305 02); P= 3 Total 33 34 112 24 15 20 34	4.5% 12.0% 100.0% 57% 16.0% 17.8% 21.9% 12.6% 5.0% 0.0% 8.3%	0.03 [0.00, 0.65] 0.07 [0.02, 0.30] 0.22 [0.11, 0.43] 0.42 [0.11, 0.43] 0.45 Ratio M-H, Random, 95% C1 0.09 [0.03, 0.29] 0.50 [0.19, 1.31] 0.53 [0.30, 0.94] 0.53 [0.00, 1.68] 0.38 [0.00, 1.68] 0.38 [0.00, 1.68]	doss, oil to Favours (Pre-op /KB) Codes Ratio M44, Random, 99% CI	200
Modarres 2009 Zaman 2013 Total (95% C) Total revents Heterogeneik, Tau? = 0.50, Test for overall effect Z = 4. <u>Study or Subgroup</u> Ahmaden 2009 Ahm 2011 De Healany 2009 Hermandez Da Mola 2010 Manake 2015 Modarres 2009 Zaman 2013	0 3 62 Chi ^p = 16. 38 (P < 0.0 Pre-op Events 13 29 3 0 4 1 3 0 4 1 3	22 24 319 46, df= 1001) IVB Total 35 36 102 48 15 20 32 22 24	7 20 141 7 (P = 0.0 <u>Events</u> 26 18 48 6 4 8 8 8 8 8 7 20	18 30 305)2); I ² = 3 Total 33 34 112 24 15 20 34 15 20 34 15 20 34 33 34 112 24 15 20 34 30 34 30 34 33 34 34 34 35 34 35 34 34 35 34 35 34 35 34 35 36 36 36 36 36 36 36 36 36 36	4.5% 12.0% 100.0% 57% 57% 16.0% 17.8% 21.9% 12.6% 5.0% 0.0% 8.3% 5.2% 13.2%	0.03 (0.00, 0.65) 0.07 (0.02, 0.30) 0.22 (0.11, 0.43) 0.44, Random, 95% (1 0.09 (0.33, 0.29) 0.50 (0.13, 0.29) 0.50 (0.13, 0.29) 0.53 (0.03, 0.54) 0.20 (0.05, 0.59) 0.38 (0.09, 1.54) 0.39 (0.00, 1.69) 0.38 (0.09, 1.54) 0.39 (0.00, 1.69) 0.39 (0.00, 0.54)	0.005 0.1 00 Favours [Pie-top /r8] MH, Random, 95% CI	200
Modarres 2009 Zaman 2013 Total (95% C) Total events Heterogenety: Tau" = 0.50; Heterogenety: Tau" = 0.	0 3 Chi ^p = 16. 38 (P < 0.0 Pre-op 9 13 29 3 0 4 1 0 3 0 4 1 0 3	22 24 319 46, df = 1001) WB Total 35 36 102 48 15 20 32 22 24 314	7 20 141 7 (P = 0.0 <u>Events</u> 26 18 48 6 4 8 8 7 20	18 30 305 305 302); *= 3 3 3 4 112 24 15 20 34 15 20 34 30 300	4.5% 12.0% 100.0% 57% Weight 16.0% 17.8% 5.0% 0.0% 8.3% 5.2% 13.2% 100.0%	0.03 (0.00, 0.65) 0.07 (0.02, 0.30) 0.22 (0.11, 0.43) 0.42 (0.11, 0.43) 0.90 (0.3, 0.25) 0.50 (0.13, 0.31) 0.50 (0.13, 0.31) 0.50 (0.13, 0.31) 0.50 (0.13, 0.31) 0.50 (0.10, 0.13) 0.50 (0.10, 0.15) 0.50 (0.10, 0.53) 0.51 (0.00, 0.45) 0.51 (0.00, 0.45) 0.51 (0.00, 0.45) 0.51 (0.00, 0.45)	0005 0.1 0 Favours (Pro-op fv8) 0006 Ratio M44, Random, 95% Cl	200
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Modares 2009 Zaman 2019 Teat (954 C) Total events List events total ev	0 0 3 62 Chi ^p = 16, 638 (P < 0.0. Pre-op Events 9 13 33 588 Chi ^p = 17, 78 588 Chi ^p = 17, 79 < 0.0. Pre-op 13 37 (P < 0.0. Pre-op 13 37 (P < 0.0. 9 13 37 (P < 0.0. 9 13 13 14 15 16 17 17 17 17 18 18 19 13 13 13 13 13 13 13 13	22 24 319 46, df = 1001) WB Total 35 36 102 48 102 48 102 22 24 314 314 314 316 10001) WB Total 35 36 36 102 48 314 319 32 22 24 24 319 319 35 36 36 36 36 36 36 36 36 36 36 36 36 36	141 7 (P = 0.1 26 18 26 18 8 8 6 4 8 8 6 4 8 8 6 4 8 8 7 7 20 137 7 (P = 0.1 20 137 7 (P = 0.1 20 20 20 20 20 20 20 20 20 20 20 20 20	318 30 305 302); F= 3 33 34 112 24 15 20 34 15 20 30 300 300 300 22); F= 3 3 4 15 20 34 15 20 16 20 30 30 30 30 30 30 30 30 30 3	4 5% 12.0% 100.0% 57% Weight 18.0% 21.9% 12.8% 5.0% 0.0% 5.2% 13.2% 100.0% 5.5% 13.2% 100.0% 5.5% 11.8% 4.4% 12.5%	0.03 (0.00, 0.85) 0.07 (10.02, 0.30) 0.22 (0.11, 0.43) 0.441 (Random, 95% (1 0.50) (0.01, 0.13) 0.50 (1.03, 0.13) 0.50 (1.03, 0.13) 0.50 (1.03, 0.13) 0.50 (1.03, 0.13) 0.50 (1.03, 0.13) 0.30 (1.00, 0.15) 0.30 (1.00, 0.15) 0.50 (1.00, 0.15) 0.50 (1.00, 0.15) 0.50 (1.00, 0.15) 0.50 (1.00, 0.15) 0.30 (0.055 0.1 0.0 Favours (Pre-op /KB) Favours (Pro-horkB) Favours (Pro-horkB) 0.065 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.005 0.1 0.0 0.1 0.1 0.0 0.1 0.1 0.0 0.1 0.1 0.0 0.1 0.1 0.0 0.1 0.1 0.0	200
Modarere 2009 Zaman 2019 Teat (954 C) Total events List events Admassing 2009 Admassing 2009 E-1000 E-1000 E-1000 Arrendo 2019 Arrendo 2019 Caman 2019 Total events Helerogeneric 7 Lan = 0.50; Teat Consult direct 2 = 4 Teat (954 C) Teat Consult direct 2 = 4 Annasidin 2009 Annasidin 2009 Annasidin 2009 Teat Consult direct 2 = 4 Study or Study or Study or Study or Study or Study Annasidin 2009 Annasidin 2009 E-1000 E-1000 Anna 2019 De 1000 E-1000 Anna 2019 De 1000 Anna 2019 De 1000 De 10000 De 100000 De 100000 De 10000000 De 1000000000000000000000000000000000000	0 0 3 62 Chi ^a = 16.638 9 <u>Events</u> 9 13 3 29 3 3 29 3 3 0 4 4 1 0 3 58 Chi ^a = 16.75 29 13 3 29 3 3 58 Chi ^a = 16.75 29 13 3 29 13 3 29 13 3 29 13 3 29 14 15 16 16 17 16 16 17 16 16 17 16 16 17 16 16 17 16 16 16 16 16 16 16 16 16 16	22 24 319 46, df = 0001) IVB 70tal 35 36 102 24 8 15 20 20 22 24 314 10, df = 102 24 314 10, df = 10001) IVB 35 36 36 102 24 314 314 314 314 32 22 24 319 32 22 24 319 32 22 24 319 32 22 24 319 32 22 24 319 32 22 22 24 319 32 22 22 24 319 32 22 22 24 319 32 22 22 24 319 32 32 22 22 24 319 32 32 22 22 24 319 32 32 22 22 24 319 32 32 22 22 24 319 319 32 32 32 32 32 32 32 32 32 32 32 32 32	141 147 (P=0.0 No IV/V Events 266 48 8 8 8 7 20 No IV/V Events 26 26 26 48 8 8 8 8 7 20 137 7 (P=0.0 137 7 (P=0.0 137 137 137 20 137 137 137 20 137 137 137 20 137 137 137 137 137 137 137 137	318 30 305 305 302); *= 3 Total 33 4 112 24 155 20 34 112 24 155 20 34 112 24 155 20 20; *= 3 3 4 112 24 30 300 28 5 20 24 24 24 24 24 24 24 24 24 24	4 5% 12.0% 100.0% 57% Weight 16.0% 21.9% 52% 12.8% 52% 13.2% 50% 0.0% 52% 13.2% 4.4% 15.3% 4.4% 12.5% 4.4% 12.3%	0.03 (0.00, 0.85) 0.07 (10.02, 0.39) 0.22 (0.11, 0.43) 0.42 (0.11, 0.43) 0.44 (Ramform, 05% C1 0.59 (10.03, 0.5%) 0.59 (10.03, 0.5%) 0.59 (10.03, 0.5%) 0.59 (10.03, 0.5%) 0.59 (10.03, 0.5%) 0.38 (10.03, 0.5%) 0.38 (10.03, 0.5%) 0.39 (10.03,	0005 01 10 Favours IPG-op MBI Favours IPG MBI Odds Ratio MH, Random, 99% CI Favours IPG-op MBI Favours IPG MBI Favours IPG-op MBI Favours IPG MBI Odds Ratio	200
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	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl	
Ahn 2011 Armula 2018	3	36	3	34	0.0%	0.94 [0.18, 5.01]		
di Lauro 2010	1	48	20	24	6.0%	0.23 [0.02, 2.72]		
El-Batarny 2008 Farahvash 2011	1	15 18	2	15 17	4.3% 2.2%	0.46 [0.04, 5.75] 0.94 [0.05, 16.35]		
Hernandez-Da Mota 2010 Manaha 2015	1	20	4	20	8.7%	0.21 [0.02, 2.08]		
Modarres 2009	1	22	1	18	2.4%	0.81 [0.05, 13.92]		
Rizzo 2008	0	11	2	11	5.5%	0.17 [0.01, 3.88]		
Total (95% CI) Total events	15	268	47	251	100.0%	0.28 [0.15, 0.52]	•	
Heterogeneity: Chi# = 2.11,	df = 7 (P =	0.95); I	*= 0%				0.01 0.1 1 10	100
Test for overall effect. Z = 4.	.08 (P < 0.0	,001)					Favours [Pre-op IVB] Favours [No IVB]	
Study or Subgroup	Pre-op Events	Total	No IV Events	B Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl	
Ahn 2011	3	36	3	34	12.8%	0.94 [0.18, 5.01]		
di Lauro 2010	9	48	28	24	11.8%	0.23 [0.02, 2.72]		
El-Batarny 2008 Farahyash 2011	1	15 18	2	15 17	8.4% 4.4%	0.46 [0.04, 5.75]		
Hernandez-Da Mota 2010	1	20	4	20	17.2%	0.21 [0.02, 2.08]		
Modarres 2009	1	22	1	18	4.8%	0.81 [0.05, 13.92]		
Rizzo 2008	0	11	2	11	10.8%	0.17 [0.01, 3.88]	·	
Total (95% CI)		202	22	173	100.0%	0.36 [0.16, 0.79]	•	
Heterogeneity: Chi ² = 3.55,	df = 7 (P =	0.83); I	= 0%				0.01 01 1 10	100
Test for overall effect: Z = 2.	.55 (P = 0.0	01)					Favours [Pre-op IVB] Favours [No IVB]	100
Study or Subaroup	Pre-op Events	IVB Total	No IV Events	B Total	Weight	Odds Ratio M-H. Fixed, 95% CI	Odds Ratio M-H. Fixed, 95% Cl	
Ahn 2011	3	36	3	34	6.5%	0.94 [0.18, 5.01]		
di Lauro 2010	9	102	28	24	0.0%	0.29 [0.13, 0.65] 0.23 [0.02, 2.72]		
El-Batarny 2008 Earahyach 2011	1	15	2	15	4.3%	0.46 [0.04, 5.75]		
Hemandez-Da Mota 2010	1	20	4	20	8.7%	0.21 [0.02, 2.08]		
Manabe 2015 Modarres 2009	1	32	1	34 18	15.0%	0.12 [0.01, 1.08] 0.81 [0.05, 13.92]		
Rizzo 2008	0	11	2	11	5.5%	0.17 [0.01, 3.88]	·	
Total (95% CI)		256		261	100.0%	0.33 [0.18, 0.58]	◆	
Total events Heterogeneity: Chi ^a = 3.69,	17 df=7(P=	0.81);1	48 *= 0%					100
Test for overall effect: Z = 3.	.78 (P = 0.0	0002)					Favours [Pre-op IVB] Favours [No IVB]	100
	Pre-op	IVB	No IV	В		Odds Ratio	Odds Ratio	
Ahn 2011	Events 3	36	Events 3	10tal 34	6.3%	0.94 [0.18, 5.01]	M-H, Fixed, 95% CI	
Arevalo 2019 di Lauro 2010	9	102	28	112	54.6%	0.29 [0.13, 0.65]		
El-Batarny 2008	1	15	2	15	0.0%	0.46 [0.04, 5.75]		
Farahvash 2011 Hernandez-Da Mota 2010	1	18 20	4	17 20	2.2% 8.5%	0.94 [0.05, 16.35] 0.21 [0.02, 2.08]		
Manabe 2015	1	32	7	34	14.8%	0.12 [0.01, 1.08]		
Rizzo 2008	ó	11	2	11	5.4%	0.17 [0.01, 3.88]	• • • • • • • • • • • • • • • • • • • •	
Total (95% CI)		289		270	100.0%	0.32 [0.18, 0.56]	•	
Total events	17	0.011	48					
Test for overall effect: Z = 3.	.90 (P < 0.0	0.01)	= 0.%				0.01 0.1 1 10 Favours IPre-op IVB1 Favours INo IVB1	100
	Pre-op	IVB	No IV	в		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Arevalo 2019	9	102	28	112	53.5%	0.29 [0.13, 0.65]		
di Lauro 2010 El-Batarry 2008	1	48 15	2	24 15	5.7% 4.1%	0.23 [0.02, 2.72]		
Farahvash 2011	1	18	1	17	0.0%	0.94 [0.05, 16.35]		
Manabe 2015	1	32	4	20	8.4% 14.5%	0.12 [0.01, 1.08]		
Modarres 2009 Rizzo 2008	1	22	1	18	2.3%	0.81 [0.05, 13.92]	· · · · · · · · · · · · · · · · · · ·	
Total (05% CI)		296	-	269	100.0%	0 21 10 17 0 551		
Total (95% CI)		280		208	100.0%	0.31[0.17, 0.55]	-	
i utai eventis	17		49					
Heterogeneity: Chi ² = 3.25, Test for overall effect 7 = 3	17 df = 7 (P = 98 (P < 0 f	0.86); I	49 *= 0%				0.01 0.1 10	100
Heterogeneity: Chi ^a = 3.25, Test for overall effect: Z = 3.	17 df = 7 (P = 98 (P < 0.0	0.86); I 0001)	49 P= 0%	D		Odda Patia	0.01 0.1 1 10 Favours [Pre-op IVB] Favours [No IVB]	100
Heterogeneity: Chi ^a = 3.25, Test for overall effect: Z = 3. Study or Subgroup	17 df = 7 (P = .98 (P < 0.0 Pre-op Events	0.86);)001) IVB Total	49 *= 0% No IV Events	B Total	Weight	Odds Ratio M-H, Fixed, 95% CI	0.01 0.1 10 Favours [Pre-op IVB] Favours [No IVB] Odds Ratio M-H, Fixed, 95% CI	100
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Heterogeneily: Chi ² = 3.25, Test for overall effect: Z = 3. Study or Subgroup Ahn 2011 Arevalo 2019 di Lauro 2010 Ci Detney 2000	17 df = 7 (P = 98 (P < 0.0 Pre-op Events 3 9 1	0.86);1 0001) IVB Total 36 102 48	49 *= 0% No IV Events 3 28 2 2	B Total 34 112 24	Weight 6.6% 57.1% 6.1%	Odds Ratio M-H, Fixed, 95% CI 0.94 (0.18, 5.01) 0.29 (0.13, 0.65) 0.23 (0.02, 2.72)	0.01 0.1 10 Favours [Pre-op IVB] Favours [No IVB] Odds Ratio M-H, Fixed, 95% CI	100
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Teleforgiana, Chi*a 326, Test for overall effect 2-a 3 Ann 2011 Ann 2011 Bestature 2010 Bestature 2010 Bestature 2010 Bestature 2010 Telai 2010 Telai 2010 Telai 2010 Telai 2010 Telai 2010 Bestature 2010 Telai 2010 Bestature 2010 Be	$\begin{array}{c} df = 7 \ (P = 0 \\ 9 \ (P < 0.) \\ Events \\ \hline \\ 3 \\ 9 \\ 0 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$	0.86); i) Total Total 36 102 48 15 18 20 32 22 11 284 0.82); i) 0002) WB Total 102 48 15 18 20 0.82); i) 0002) WB 20 22 22 11 284 15 1002 22 22 11 284 15 1002 22 22 11 284 15 1002 22 22 11 284 15 1002 22 22 11 284 15 1002 100	49 49 49 40 50 50 50 50 50 50 50 50 50 5	B Total 34 112 24 15 17 265 B Total 34 112 265 B Total 34 112 265 B Total 34 112 265 B Total 34 15 17 265 8 Total 34 15 17 265 8 Total 34 15 17 265 8 Total 112 24 15 17 265 17 20 17 17 20 17 17 20 17 17 20 17 17 17 20 17 17 17 17 17 17 17 17 17 17	Weight, 6.6%, 6.1%, 4.2.3%, 15.4%, 5.6%, 15.4%, 61.1%, 4.7%, 2.6%, 4.7%, 2.6%, 100.0%, 10	0455 Ratio 0.945 Ratio 0.94 (01.5, 501 0.22 (01.2, 627 0.24 (01.2, 627	0.01 0.1 0.1 0.00 Favours [Pit-op /K8] 0.01 0.1 0.00 Favours [Pit-op /K8] 0.01 0.1 0.00 Favours [Pit-op /K8] 0.00 Favours [Pit-op /K8] Favours [Pit-op /K8] 0.00 Favours [Pit-op /K8] 0.00 Favours [Pit-op /K8] Favours [Pit-op /K8] 0.00 Favours [Pit-op /K	100
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Teleforgana, Ch ²⁺ 3 25, Test for overall effect 2 - 3 Min 2011 Ann 2011 Elevation of the second effect 2 - 3 Ann 2011 Elevation of the second effect 2 - 3 Ann 2011 Elevation of the second effect 2 - 3 Minable 2016 Herenagenet? Ch ² = 3.81, Herenagenet? Ch ² = 2.80, Rizz - 2008 Table 2016 Herenale 201	$\begin{array}{c} df = 7 \ (P = 0 \\ 9 \ (P < 0.0 \\ P \\ P \\ P < 0.0 \\ P \\ P \\ P < 0.0 \\ P \\ $	0.86);1 0001) IVB Total 36 1022 48 48 15 18 20 022 221 IDE Total 36 102 48 15 18 20 022 21 IDE Total 36 102 48 15 18 20 0022 IDE Total 36 102 48 15 18 20 0022 IDE Total 36 102 48 15 102 221 10002 IDE 10002 IDE 102 48 15 16 102 48 15 102 221 11 IDE 102 48 15 102 221 11 IDE 10002 IDE 1002 102 48 15 102 48 15 102 48 15 102 222 11 IDE 102 48 15 15 16 102 48 15 15 16 102 48 15 15 16 102 48 15 15 16 102 48 15 15 15 15 15 15 15 15 15 15	*= 0% No IV Events 3 3 2 2 2 2 1 1 4 4 7 7 1 2 8 8 0% No IV Events 3 2 8 2 9 2 2 1 1 4 7 7 1 2 8 8 8 2 9 2 2 2 1 1 1 4 7 7 1 2 8 8 8 8 8 8 9 8 9 8 9 8 9 8 9 8 9 8 9	B Total 34 112 22 34 15 7 200 34 11 265 Total 34 11 251 B Total 34 11 251 B Total 34 11 251 B Total 34 11 251 251 251 251 251 251 251	Weight 6.8% 57.1% 4.4% 2.3% 0.0% 5.6% 100.0% Weight 4.7.1% 6.6% 4.7% 2.5% 6.0% 6.0% 100.0% Weight 4.4% 0.0% 0.0% 100.0%	0455 Ratio 0.9455 Ratio 0.94 [01, 501] 0.22 [01, 02] 0.22 [01, 02] 0.22 [01, 02] 0.23 [01, 02] 0.24 [00, 12] 0.24 [00, 12] 0.24 [00, 12] 0.24 [00, 12] 0.24 [00, 12] 0.31 [00, 132] 0.33 [0, 19] 0.46 [00, 132] 0.46 [00, 132] 0.47 [00, 136] 0.48 [00, 132] 0.48 [00, 132]	0.01 0.1 0.1 0.04 Ratio Favours (Pic-op Nil) Favours (Pic-Nil) 0.01 0.1 0.1 0.04 Ratio Nil Fixed, 95% Cl 0.01 0.1 0.1 0.04 Ratio Mil, Fixed, 95% Cl 0.03 0.1 0.1 0.04 Favours (Pic-Nil) 0.04 Ratio Mil, Fixed, 95% Cl 0.04 Ratio Mil, Fixed, 95% Cl	100
Teleforginal, Ch ²⁺ = 3.25, Test for overall effect 2 = 3. 2015 Constraints of the constraint of the constraints Ann 2011 Constraints of the constraints Ann 2011 Constraints of the constraints of the constraints of the constraints of the constraints of the constraints Modares 2008 Telai (Sric Ch Tolai events Heterogenetic) Ch ²⁺ = 3.61, 3.51, 2	$\begin{array}{c} df = 7 \ (P = 0 \\ 98 \ (P + 0.0 \\ Free op \\ \hline Events \\ 3 \\ 3 \\ 9 \\ 9 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$	0.86); 1) 10001) Total Total 3 3 4 8 4 8 2 2 2 2 2 2 2 2 2 2 2 2 2	*= 0% No IV Events 3 28 29 20 20 20 20 20 20 20 20 20 20	B Total 34 112 24 15 7 200 34 11 265 Total 34 11 265 Total 34 11 251 B Total 34 11 251 B Total 34 11 265 34 11 265 34 11 265 34 11 265 34 11 265 17 20 34 11 265 17 20 34 11 265 17 20 34 11 265 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 17 20 34 11 12 25 17 20 34 11 12 25 17 20 34 11 25 17 20 34 11 25 17 20 34 11 25 17 20 24 16 17 20 34 11 25 17 20 34 11 25 17 20 20 34 11 25 17 20 20 34 11 25 17 20 20 34 11 25 17 20 20 34 11 25 17 20 20 34 11 22 24 24 15 17 20 20 34 11 22 24 24 15 17 20 20 34 11 22 24 24 15 17 20 24 15 17 20 24 15 17 20 20 20 16 16 16 16 16 16 16 16 16 16	Weight 6.8% 57.1% 4.4% 2.5% 5.6% 5.6% 61.1% 7.1% 61.1% 6.1% 4.7% 2.5% 6.8% 6.5% 6.5% 6.5% 5.8% 5.8% 5.8% 5.8% 5.8% 5.8% 5.8% 100.0% 100.0%	0445 Ratio 0.445 Ratio 0.44 (1764, 557) 0.47 (101, 501) 0.47 (101, 501) 0.47 (101, 501) 0.47 (101, 501) 0.47 (101, 501) 0.47 (101, 201) 0.47 (101, 201) 0.47 (101, 201) 0.47 (101, 201) 0.47 (101, 201) 0.48 (101, 501) 0.48 (101, 501	0.01 0.1 0.1 0.00 Favours [No Nd] 0.01 0.1 0.1 0.00 Favours [No Nd] 0.01 0.1 0.1 0.00 Favours [No Nd] 0.01 0.1 0.1 Favours [No Nd] 0.01 0.1 0.1 Favours [No Nd] 0.01 0.1 0.1 0.00 Favours [No Nd] 0.01 0.1 0.1 0.00 Favours [No Nd] 0.01 0.1 0.1 0.00 Favours [No Nd] 0.01 0.1 0.0 Favours [No Nd] 0.01 0	100 ⁴
Inderengenay, Ch ²⁺ 3 25, Test for overall effect 2 - 3 Test for overall effect 2 - 3 Ana 2011 All 2010 All 20	$\begin{array}{c} df = 7 \ (\mathcal{P} = 0 \\ 98 \ (\mathcal{P} < 0.0 \\ 1 \\ 98 \ (\mathcal{P} < 0.0 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ $	0.86); 1) 10001) Total Total 366 102 48 48 20 22 21 1 284 0.82); 1) 0002) WB Total 366 102 48 48 20 22 21 1 284 0.82); 1) 0002) WB Total 366 102 284 102 284 102 284 102 100 102 11 284 102 100 102 102 102 102 102 102	*= 0% No IV Events 3 28 22 2 2 2 2 2 2 2 2 2 2 2 2	B Total 34 112 24 15 17 20 34 18 11 265 8 Total 34 112 251 34 112 24 15 17 20 34 34 112 251 34 112 251 34 112 251 34 112 265 267 20 20 20 20 20 20 20 20 20 20 20 20 20	Weight t 6.8% 57.1% 4.4% 2.5% 100.0% Weight t 6.2% 6.0% 6.0% 5.8% 5.8% 5.3% 5	0445 Ratio 0.94 (11, 501) 0.24 (10, 51, 502) 0.24 (10, 51,	bot di response priori processi priori di francessi priori di fran	100 ⁴
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Teleforegain, Ch ² = 325, Test for overall effect 2 = 3 Ana 2011 Ana 2011 Ana 2010 Ana 2010 Ana 2010 Ana 2010 Ana 2010 Ana 2010 Ana 2010 Ana 2010 Telai 2003 Telai 2003 Telai 2003 Telai 2003 Telai 2003 Telai 2003 Chai 2003 Telai 2003 Chai 2003	$\begin{array}{c} qr = 1^{rr} \\ qr = 1^{r$	0.86);1 MB Total 3 3 4 4 2 4 4 5 102 4 8 2 2 2 11 2 8 4 102 4 8 2 2 2 11 2 8 4 8 102 4 8 102 4 8 102 2 2 2 11 2 8 4 8 102 2 2 2 11 2 8 4 8 102 2 2 2 11 2 8 4 8 102 2 2 2 2 11 2 8 4 8 102 2 2 2 2 11 2 8 4 8 102 2 2 2 2 11 1 2 8 4 8 102 2 2 2 2 11 1 2 8 4 8 102 2 2 2 2 11 1 2 8 4 8 102 2 2 2 2 11 1 2 8 4 8 102 2 2 2 11 1 2 8 4 8 15 102 2 4 8 102 2 2 2 11 1 2 7 2 2 2 11 1 2 7 2 2 2 11 1 2 7 2 2 2 11 1 2 7 2 2 2 11 1 2 7 2 2 2 11 2 7 2 2 2 11 2 7 7 7 7 7 7 7 7 7 7 7 7 7	*=0% No IV Events 28 29 20 20 20 20 20 20 20 20 20 20	B Total 34 12 24 12 24 17 20 34 11 265 17 20 34 112 24 112 112	Weight 6.6% 571% 6.6% 571% 15.4% 15.4% 15.4% 15.4% 15.4% 15.4% 15.4% 15.4% 15.4% 100.0% Weight 100.0% Weight 14.5% 100.0% Weight 14.5% 0.0% 5.3% 100.0% Weight 105.64% 5.4% 5.4% 5.4%	0445 Ratio 0.445 Ratio 0.44 (1764, 597, 617, 591 0.248 (13,	0.01 0.1 0.1 0.005 Raio 0.01 0.1 0.1 0.005 Raio 0.01 0.1 0.1 0.0 Favours [No NE] 0.01 0.1 0.1 0.1 0.0 Favours [No NE] 0.01 0.0 Favours [No NE]	100
Teleforgiana, Ch ² = 3.25, Test for overall effect 2 = 3. Why or Shagroup Am 2011 di Law 2010 E Shafarry 2001 di Law 2010 E Shafarry 2001 Hemandez Da Mola 2010 Modares 2009 Total effs Ch Total events Heterogenetic, Ch ² = 3.61, Heterogenetic, Ch ² = 2.60, Rizzo 2008 Total events Heterogenetic, Ch ² = 2.60, Total events Heterogenetic, Ch ² = 2.60, Total events Heterogenetic, Ch ² = 2.61, Total events Heterogenetic, Ch ² = 2.61, Key or Shagroup An 2011 An 2011 An 2010 E Shafarry 2005 Heterogenetic, Ch ² = 2.61, Key or Shagroup	$\begin{aligned} & g = 1^{T} \\ g = 0 \\ g = $	0.86);1 10001) Total Total 102 48 102 48 102 48 102 48 102 282 222 11 284 0.82); 100 70 70 70 70 70 70 70 70 70	No IV P 0% No IV Events 3 28 2 2 1 46 7 7 7 3 8 2 2 1 2 2 1 46 7 7 7 1 2 2 1 4 4 4 4 7 7 1 2 2 2 1 2 2 2 1 2 2 2 1 2 2 2 1 2 2 2 1 2 43 3 3 3 3 3 3 3 2 2 2 2	B Total 34 12 12 24 17 17 265 Total 34 11 265 17 266 17 266 17 266 17 266 17 266 17 266 17 266 17 266 17 266 17 266 17 266 17 17 266 17 17 266 17 17 266 17 17 17 17 17 17 17 17 17 17	Weight 6.65% 57.1% 4.45% 5.5% 15.4% 7.1% 6.6% 7.1% 6.6% 5.2% 7.1% 6.6% 6.2% 5.36% 4.1% 2.6% 6.2% 5.3% 100.0% Weight 4.1% 0.0% 5.3% 14.5% 5.4% 4.1% 5.3% 4.1% 5.3% 4.1% 5.3% 4.1% 5.4% 6.5% 5.4% 6.4% 5.4%	045 Ratio 0.45 Ratio 0.94 (116, 501) 0.22 (012, 022) 0.22 (012, 022) 0.21 (012, 021) 0.21 (012, 021) 0.21 (012, 021) 0.41 (025, 1322) 0.41 (025, 13	0.01 0.1 0.1 0.04 Relia 0.04 Relia 0.05 Relia 0.05 Relia 0.05 Relia 0.01 0.1 0.1 0.04 Relia 0.01 0.1 0.04 Relia 0.05 Re	100 ¹
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Figure 19. Sensitivity analyses of preoperative IVB effect on requirement for revision vitrectomy.

Manabe et al., which reported a statistically insignificant reduction in surgical time from preoperative IVB, all other studies showed a beneficial effect of IVB. Our analysis provides an overall estimate of the magnitude of preoperative IVB in reducing surgical time. This finding may be the result of the regression of neovascularization, reducing intraoperative bleeding, allowing improved visualization of the surgical field and easier surgical manipulations. These results are in accordance with the findings of previous observational studies.⁵⁴ Aiming to find the optimal time frame for the administration of IVB, Castillo et al. conducted an RCT, assigning patients to receive IVB either 5–10 days or 1–3 days before surgery.⁵⁵ They found that the administration of IVB 5-10 days prior to vitrectomy had statistically significantly better outcome regarding BCVA. However, there was no difference between groups in intraoperative complications and surgical time, a result compatible with our subgroup analyses.

Concerning the effect of preoperative IVB on the occurrence of iatrogenic intraoperative retinal breaks, data from 6 RCTs were included in this review. The present analysis suggests that preoperative IVB reduces the occurrence of retinal breaks intraoperatively. Again, this may be related with better retina view intraoperatively, allowing for easier segmentation and delamination of fibrovascular membranes, and thus reducing the risk of intraoperative complications. This finding is corroborated by the results of an observational study reporting less intraoperative bleeding in patients receiving preoperative IVB.²⁷

This review suggests that preoperative IVB provides better BCVA in the long term. However, this comparison may be subject to substantial heterogeneity. Diverse factors including lens opacities, macular edema, retinal comorbidities and optic nerve status may all affect visual acuity, as well as the duration of the follow-up. However, when controlling for baseline visual acuity, the performance of combined phacovitrectomy versus vitrectomy alone and the time of the last follow-up visit, no statistically significant correlation was found. Better visual outcomes in patients receiving preoperative IVB were also reported in a subgroup analysis of the DRIVE-UK study. The authors were also able to show that preoperative IVB had a protective effect on the development of diabetic macular edema at 12 months postoperatively.23,56

	Pre-op IVB No IVB						Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Arevalo 2019	71.3	32.1	102	83.6	38.7	112	16.5%	-12.30 [-21.80, -2.80]	_
di Lauro 2010	67	19.45	48	84	12	24	19.6%	-17.00 [-24.30, -9.70]	
El-Batarny 2008	61.6	14.5	15	93.3	11.6	15	16.6%	-31.70 [-41.10, -22.30]	_
Faisal 2018	64.1	10.35	28	80.5	10.22	28	22.4%	-16.40 [-21.79, -11.01]	
Hernandez-Da Mota 2010	62	31	20	98	35	20	6.9%	-36.00 [-56.49, -15.51]	
Manabe 2015	49	20	32	56	27	34	0.0%	-7.00 [-18.42, 4.42]	
Modarres 2009	62	57.3	22	95.5	36	18	0.0%	-33.50 [-62.65, -4.35]	
Rizzo 2008	57	9	11	83	11	11	18.0%	-26.00 [-34.40, -17.60]	
Total (95% CI)			224			210	100.0%	-21.46 [-27.68, -15.25]	•
Heterogeneity: Tau ² = 37.44	; Chi ² = 1	15.14, d	f= 5 (P	= 0.010	0); I ² = 6	7%			
Test for overall effect: Z = 6.7	77 (P < 0	.00001)						-50 -25 0 25 50 Favours (pre-op IVB) Favours (No IVB)

Figure 20. Sensitivity analysis of the effect of preoperative IVB 1.25 mg/0.05 mL on operation time.

	Pre-op	IVB	No IV	/B		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl		
Ahmadieh 2009	2	35	1	33	1.6%	1.94 [0.17, 22.46]			
Arevalo 2019	35	102	66	112	69.7%	0.36 [0.21, 0.63]			
di Lauro 2010	1	48	4	24	8.8%	0.11 [0.01, 1.01]			
Faisal 2018	2	28	8	28	12.5%	0.19 [0.04, 1.01]			
Manabe 2015	5	32	5	34	0.0%	1.07 [0.28, 4.13]			
Rizzo 2008	0	11	4	11	7.3%	0.07 [0.00, 1.55]	←		
Total (95% CI)		224		208	100.0%	0.32 [0.20, 0.53]	•		
Total events	40		83						
Heterogeneity: Chi ² =	4.46, df=	4 (P =	0.35); I ^z =	:10%					
Test for overall effect:	Z= 4.58 ((P < 0.0	0001)				Favours [Pre-op IVB] Favours [No IVB]		

Figure 21. Sensitivity analysis of the effect of preoperative IVB 1.25 mg/0.05 mL on iatrogenic intraoperative retinal breaks.



Figure 22. Sensitivity analysis of the effect of preoperative IVB 1.25 mg/0.05 mL on best-corrected visual acuity at the last follow-up visit.

Nine studies were used to assess the effect of preoperative IVB on postoperative VH. Preoperative IVB was proven to be effective in reducing the incidence of postoperative VH. The use of silicone oil tamponade in the studies of Arevalo et al., Di Lauro et al., El Batarny et al., Manabe et al., Modarres et al., and Zaman et al., may have inf the results, by masking the effect of recurrent VH.⁵⁷ However, a sensitivity analysis, with these studies excluded showed the same effect. The protective effect of preoperative IVB on recurrent VH has been recognized in the literature.^{24,25,28,58,59} In a previous Cochrane review, it was reported that preoperative IVB was effective in reducing early VH but not late.²⁹ However, our results suggest that IVB may protect from recurrent VH regardless of time. The perhaps paradoxical reduction in late recurrent VH we report may be due to more effective traction release during

	Pre-op	IVB	No IV	B		Odds Ratio	Odds Ratio
Study or Subgroup	Events	lotal	Events	lotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ahmadieh 2009	9	35	26	33	16.0%	0.09 [0.03, 0.29]	-
Ahn 2011	13	36	18	34	18.2%	0.50 [0.19, 1.31]	
Arevalo 2019	29	102	48	112	23.5%	0.53 [0.30, 0.94]	
di Lauro 2010	3	48	6	24	12.2%	0.20 [0.05, 0.89]	
El-Batarny 2008	0	15	4	15	4.4%	0.08 (0.00, 1.69)	
Hernandez-Da Mota 2010	4	20	8	20	12.9%	0.38 [0.09, 1.54]	
Manabe 2015	1	32	8	34	0.0%	0.10 [0.01, 0.89]	
Modarres 2009	0	22	7	18	0.0%	0.03 (0.00, 0.65)	
Zaman 2013	3	24	20	30	12.7%	0.07 [0.02, 0.30]	
Total (95% CI)		280		268	100.0%	0.24 [0.12, 0.48]	•
Total events	61		130				_
Heterogeneity: Tau ² = 0.44; (Chi ² = 13.	93, df=	6 (P = 0.	03); l² =	= 57%		
Test for overall effect: Z = 4.0	04 (P < 0.0	0001)					Favours [Pre-op IVB] Favours [No IVB]

Figure 23. Sensitivity analysis of the effect of preoperative IVB 1.25 mg/0.05 mL on postoperative vitreous cavity haemorrhage.



Figure 24. Sensitivity analysis of the effect of preoperative IVB 1.25 mg/0.05 mL on requirement for revision vitrectomy.



Figure 25. Funnel plot assessing publication bias in operation time assessment.

surgery, reducing the occurrence of late tractional related haemorrhages.⁶⁰

Finally, eight studies commented on the effect of preoperative IVB on the need for revision vitrectomy. All the analyses performed demonstrated the beneficial effect of IVB in reducing reoperation rates, regardless the cause and including tractional complications corroborating our hypothesis regarding late.

Concerning the dose of IVB, Hattori et al. reported that 0.16 mg dose was as effective as 1.25 mg in terms of reducing intraoperative bleeding.⁶¹ In another RCT by Castillo-Velazquez et al., which assessed three different doses, no statistically significant difference was found in terms of final BCVA and postoperative complications.⁶² However, they suggested that patients receiving the minimum dose for efficacy (0.625 mg) had a lower incidence of TRD compared with the other two groups (1.25 mg and 2.5 mg). Our sensitivity analyses, including doses of 0.16 mg, 1.25 mg and 2.5 mg, also suggest that the beneficial effect of preoperative IVB is independent of dose. However, concerning the findings of Castillo-Velazquez et al., doses of IVB should be kept to a minimum efficient concentration in order to prevent TRD.

Three other systematic reviews have been published on this topic including a Cochrane review which primarily assessed the effect on POVCH.29-31 Nevertheless, the publication of two new studies,^{38,41} one of which is the largest in this subject, a retracted paper in the previous meta-analysis (Elwan MM, Ghanem AA, Abousamra WA. Outcome of a single intravitreal bevacizumab injection on the visual acuity and course of pars plana vitrectomy in proliferative diabetic retinopathy. Current Eye Research 2013 Sep 27) and the necessity to investigate other post- and intraoperative outcomes warranted an up to date and more comprehensive review restricted to the most commonly used agent, Bevacizumab alone.

This review presents some key strengths. The sensitivity and subgroup analyses, meta-regression models and the risk of bias assessment of the included studies, corroborate the internal validity of the results. Moreover, the inclusion of studies concerning different surgeons, with variable surgical experience and equipment and involving patients from different countries raises the external validity and applicability of the results.

We accept, however, that the present meta-analysis has several limitations. First, the majority of included studies are small (<100 subjects), thus reducing their statistical significance. Moreover, there is some diversity among studies about the indication for diabetic vitrectomy. Third, only three electronic databases were searched to retrieve relevant studies, which may mean other relevant studies were missed. The studies had variable follow-up but to adjust for this additional metaregression analyses were carried out. Disparity in the quality of individual studies was relatively minor. The study by Arevalo et al. had an adequate sample size but was multicentric, which implies potential diversity in surgical techniques and equipment, although equally well suggests broad applicability.³⁸ The high drop-out rate in the double-masked RCT by Ahmadieh et al. compromises its statistical significance.³⁶ The studies by Zaman et al., Hernandez-Da Mota et al. and Farahvash et al. lacked pre-specified analysis plans risking



Figure 26. Funnel plot assessing publication bias in iatrogenic intraoperative retinal breaks.



Figure 27. Funnel plot assessing publication bias in best-corrected visual acuity at the last follow-up visit.

selective reporting.^{42,43,48} In the study by Di Lauro et al., baseline differences between groups may have influenced results.³⁹ Similarly, baseline differences among groups and the lack of sham injections and double-masking might have affected the results in the study by Ahn et al.³⁷ The study by El-Batarny et al. was subject to bias due to the variable follow-up and lack of masking.⁴⁰ In the study by Rizzo et al., the main sources of potential biases were the relatively small sample size and the limited follow-up time.⁴⁶ A relatively short follow-up was also an issue in the study by Manabe et al.,⁴⁴ as







Figure 29. Funnel plot assessing publication bias in requirement for revision vitrectomy.

well Possible yet unavoidable lack of masking was the main risk of bias in the study by Modarres et al.⁴⁵ No masking is also a limitation in the study by Faisal et al.⁴¹ Finally, the small sample size reduces statistical significance in the study by Sohn et al.⁴⁷

Based on current evidence, the adjunctive use of preoperative bevacizumab in patients undergoing vitrectomy for PDR improves surgical feasibility by reducing operation time and the occurrence of iatrogenic retinal breaks. Besides reducing postoperative VHs and the need for a second vitrectomy, it is associated with better visual outcomes. Studies comparing different doses and timing of IVB prior to surgery would be useful additions to the evidence base.

Authors' contributions

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Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: *Professor David Steel (all unrelated to current work)*:

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Supplemental material

Supplemental material for this article is available online.

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