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Η ΣΥΜΠΛΗΡΩΜΑΤΙΚΗ ΕΝΔΟΫΑΛΟΕΙΔΙΚΗ ΧΟΡΗΓΗΣΗ ΠΡΟΕΓΧΕΙΡΗΤΙΚΑ ΜΠΕΒΑΣΙΖΟΥΜΑΜΠΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΠΟΥ ΥΠΟΒΑΛΛΟΝΤΑΙ ΣΕ ΥΑΛΟΕΙΔΕΚΤΟΜΗ ΓΙΑ ΠΑΡΑΓΩΓΙΚΗ ΔΙΑΒΗΤΙΚΗ ΑΜΦΙΒΛΗΣΤΡΟΕΙΔΟΠΑΘΕΙΑ: ΜΙΑ ΜΕΤΑ-ΑΝΑΛΥΣΗ ΚΑΙ ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΒΙΒΛΙΟΓΡΑΦΙΑΣ

THE ADJUNCTIVE USE OF PREOPERATIVE BEVACIZUMAB IN PATIENTS UNDERGOING VITRECTOMY FOR PROLIFERATIVE DIABETIC RETINOPATHY: A META-ANALYSIS AND SYSTEMATIC REVIEW OF THE LITERATURE

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CONTENTS

A. Abstract

Introduction

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. However, diabetic vitrectomy is quite a challenging operation, especially in cases of tractional retinal detachment, requiring advanced micro-surgical techniques. Adjuvant pre-operative use of intravitreal bevacizumab has been an option widely employed, with promising results in terms of increasing the feasibility of surgery and improving prognosis.

Aim

The aim of the present study is to assess the efficacy of pre-operative intravitreal bevacizumab, by providing an overall estimate that shows its effectiveness in terms of intraoperative complications and post-operative outcomes.

Methods

A meticulous literature search was conducted in the PubMed, COCHRANE and ClinicalTrials.gov databases in order to identify all related studies published before 31/8/2020. Prespecified outcome measures were operation time needed, the number of intraoperative iatrogenic retinal breaks occurred, best-corrected visual acuity in the last follow-up visit, the presence of any post-operative vitreous hemorrhage and the need for repeat vitrectomy. Evidence synthesis was performed using Fixed Effects of Random Effects model, depending on the heterogeneity of the included studies. Heterogeneity was assessed using Q-statistic and I^2. Additional meta-regression models, subgroup analyses and sensitivity analyses were performed when appropriate.

Results

Thirteen randomized control trials studying 688 eyes undergoing diabetic vitrectomy were included in this review. The comparison of the intraoperative characteristics showed that bevacizumab reduces operation time ($p<0.001$), decreases the iatrogenic retinal breaks ($p<0.001$), provides better long-term visual acuity outcomes ($p=0.005<0.05$), and prevents vitreous hemorrhages ($p<0.001$) and repeated vitrectomies ($p=0.001<0.05$). These findings presented robust in additional sensitivity and subgroup analyses.

Conclusion

Pre-operative administration of bevacizumab is quite beneficial, as it reduces intraoperative complications and provides better post-operative prognosis.

<u>Α. Περίληψη</u>

Εισαγωγή

Η διαβητική αμφιβληστροειδοπάθεια είναι μια κύρια αιτία απώλειας όρασης στη μέση ηλικία. Η υαλοειδεκτομή έχει εξελιχθεί ως η θεραπεία εκλογής της σοβαρής, παραγωγικής διαβητικής αμφιβληστοειδοπάθειας. Ωστόσο, η υαλοειδεκτομή σε πάσχοντες από διαβητική αμφιβληστροειδοπάθεια είναι μια αρκετά απαιτητική επέμβαση, ειδικά σε περιπτώσεις ασθενών επιπλεγμένες με ελκτική αποκόλληση αμφιβληστροειδούς, απαιτώντας ιδιαίτερες μικρο-χειρουργικές τεχνικές. Η συμπληρωματική προεγχειρητική ενδοϋαλοειδική χορήγηση μπεβασιζουμάμπης είναι μια ευρέως χρησιμοποιούμενη τεχνική, με ελπιδοφόρα αποτελέσματα όσον αφορά τη διεγχειριτική διευκόλυνση και τη βελτίωση της πρόγνωσης.

Στόχοι

Στόχος της παρούσας μελέτης είναι η αποτίμηση της αποτελεσματικότητας της προεγχειρητικής ενδοϋαλοειδικής μπεβασιζουμάμπης, παρέχοντας μια συνολική αποτίμηση της δράσης της όσον αφορά τις διεγχειρητικές επιπλοκές και τα μετεγχειρητικά αποτελέσματα.

Μέθοδοι

Μία σχολαστική αναζήτηση βιβλιογραφίας έγινε στις βιβλιοθήκες PubMed, Cochrane και ClinicalTrials.gov για την ανεύρεση σχετικών μελετών με ημερομηνία δημοσίευσης πριν από τις 31/8/2020. Ως αποτελέσματα ορίστηκαν εξ' αρχής η διάρκεια του χειρουργείου, ο αριθμός ιατρογενών ρωγμών αμφιβληστροειδούς, η διορθωμένη οπτική οξύτητα στην τελευταία επίσκεψη του μετεγχειρητικού ελέγχου, η παρουσία μετεγχειρητικής ενδοϋαλοειδικής αιμορραγίας και η ανάγκη για δεύτερη υαλοειδεκτομή. Η σύνθεση των αποτελεσμάτων έγινε με το μοντέλο Σταθερών Επιδράσεων ή το μοντέλο Τυχαίων Επιδράσεων, ανάλογα με την παρουσία ετερογένειας ανάμεσα στις επιμέρους μελέτες. Η ετερογένεια ελέγχθηκε χρησιμοποιώντας τη δοκιμασία Q-statistic και το I^2. Επιπρόσθετα, μετα-παλινδρομήσεις, ανάλυση ανά υπο-ομάδες και αναλύσεις ευαισθησίας εκτελέστηκαν όπου κρίθηκε σημαντικό.

Αποτελέσματα

Δεκατρείς τυχαιοποιημένες ελεγχόμενες κλινικές δοκιμές που περιλαμβάνουν συνολικά 688 οφθαλμούς που επρόκειτο να υποστούν διαβητική υαλοειδεκτομή συμπεριλήφθηκαν στην ανασκόπηση. Η σύγκριση των διεγχειρητικών χαρακτηριστικών έδειξε μείωση του χρόνου χειρουργείου ($p<0.001$), μείωση των ιατρογενών ρωγμών αμφιβληστροειδούς ($p<0.001$), ενώ μετεγχειρητικά παρείχε καλύτερη διορθωμένη οπτική οξύτητα ($p=0.005<0.05$), αποτρέποντας υαλοειδικές αιμορραγίες ($p<0.001$) και επανάληψη της υαλοειδεκτομής ($p=0.001<0.05$). Τα αποτελέσματα παρέμειναν

στατιστικά σημαντικά στις επιπρόσθετες αναλύσεις ευαισθησίας και σε αναλύσεις ανά υπο-ομάδες.

Συμπέρασμα

Η προεγχειρητική χορήγηση ενδοϋαλοειδικά μπεβασιζουμάμπης είναι αποτελεσματική, καθώς μειώνει τις διεγχειρητικές επιπλοκές και παρέχει καλύτερη μετεγχειρητική πρόγνωση.

B. Introduction

Diabetic retinopathy (DR) is a major cause of legal blindness in working-age adults.[1-3] According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy Cohort, 71%-90% of patients suffering from diabetes mellitus (DM) for more than 10 years will have some degree of DR.[4] DR consists of two different clinical entities, non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). It has been stated that 50% of patients suffering from advanced NPDR, consisting of inner retinal hypoxia, intraretinal microvascular abnormalities and large areas of capillary non-perfusion, will progress to PDR within 1 year, if left untreated.[5]

The differential characteristic of PDR compared to NPDR is the presence of neovascularization either within 1 diameter of the optic disc (NVD) or elsewhere (NVE) in the retina. These new vessels usually grow along the route of the least resistant path, like the absence of an internal limiting membrane on the optic nerve head or even a shallow posterior vitreous detachment (PVD). Moreover, connective tissue forms along the new vessels. This connective tissue helps vitreous traction to be transmitted to the retina, inducing tractional retinal detachment (TRD). NVE almost always forms in areas of retinal ischemia, until PVD occurs. Then the abnormal vessels grow to the vitreous cavity. Contraction of the vitreous and the connective tissue component of these vessels can cause vitreous hemorrhage, TRD, retinoschisis and retinal tears.

Pars plana vitrectomy (PPV) plays a vital role in the management of complications arising from PDR. Non clearing VH, macular involving or macular threatening TRD and combined tractional-rhegmatogenous RD are the main indications.[6] The main objectives of this operation is to remove the blood and vitreous gel from the vitreous cavity, to release retinal traction and to perform laser endophotocoagulation. The very challenging nature of this surgery, may be related with intraoperative complications like iatrogenic retinal breaks, prolonged operation time and intraoperative bleeding, thus worsening the prognosis.[7-9] Furthermore, in about 10% of the patients, repeat vitrectomy is required due to rhegmatogenous RD and recurrent VH.[10]

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Bevacizumab is approved by the U.S. Food and Drug Administration against cases of metastatic colorectal cancer. Off-label, Bevacizumab 1.25mg/0.05ml is also used intravitreally to halt the progression of PDR. The administration of intravitreal bevacizumab (IVB) in patients with PDR, despite its proven efficacy in the regression of neovascularization, is thought to induce contraction of the fibrovascular tissue, thus leading to TRD or to an aggravation of an existing RD.[11-13]

The adjunctive use of preoperative IVB in patients undergoing vitrectomy for severe PDR has been an interesting debate through the years in terms of balancing the risk/benefit ratio.[14, 15] However, despite its widespread use by retina specialists, there is lack of evidence regarding the effect of preoperative IVB on intraoperative complications during PPV, and on postoperative outcomes for these patients. The present review attempts to evaluate the use of preoperative IVB in patients undergoing vitrectomy for severe PDR.

C. Methods

Evidence acquisition

The present 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 guidelines.[16, 17]

Eligibility criteria

Inclusion criteria

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

- Publication date was before August 31, 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 one month before the day of surgery was planned. The control group was randomized to sham injection or no treatment.

Exclusion criteria

The following exclusion criteria were applied to our study:

- reports not published in English
- conference abstracts
- pilot trials
- retracted papers

Search method

A meticulous literature search was conducted in the PubMed, COCHRANE and ClinicalTrials.gov databases in order to identify all related studies. Furthermore, for studies retrieved, manual search in their references was performed to find possible relevant reports. The 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 a single author (P.D). For titles and abstracts of possibly eligible studies, full texts were screened.

Quality Assessment

Risk of Bias (RoB) Cochrane Tool for Systematic Reviews of Interventions was used to evaluate the retrieved RCTs.[18] RoB assesses several domains of bias, in view of trial design, conduct and reporting, as of low risk of bias, high risk of bias or unclear risk of bias.

Data extraction

The following data were retrieved from the included studies: author's name, number of subjects enrolled, indication for vitrectomy, intervention groups and outcomes measured. One independent author carried out RoB assessment and data extraction.

Outcome measures

The primary outcome measure of the present study was the intraoperative characteristics/ complications of diabetic vitrectomy in terms of operation time and iatrogenic intraoperative retinal break development. Secondary outcomes were logMAR best corrected visual acuity (BCVA) at the last follow-up visit, the presence of postoperative VH and the need for second vitrectomy regardless of the cause.

Statistical analysis

Review Manager (*Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020)* was used for all the statistical analyses. For continuous data, mean differences (MDs) and their 95% confidence intervals (95% CIs) were calculated for each time frame. For binary outcomes, Odds Ratios (ORs) and their 95% CIs were used. Fixed effects (FE) or random effects (RE) were used for data synthesis. The weight of each study was calculated as the inverse variance of individual effects. Heterogeneity among studies was tested with both the Q-statistic and I^2.[19] Heterogeneity was assumed if $P_Q<0.1$ or $I^2>50\%$. If significant heterogeneity was found, the result was based on the RE model and heterogeneity was explored with meta-regression, sensitivity analyses and subgroup analyses. Otherwise FE model was used. Publication bias was assessed with forest plot. In all comparisons, sensitivity analyses were performed with the method of leave-one-out. For the exploration of any possible heterogeneity present among studies, subgroup analyses and meta-regressions were performed.

D. Results

Study selection

The flow diagram of the study selection is presented in Table 1. Last literature search was performed on September 1st 2020. Of the 154 potentially relevant studies retrieved from electronic search and related references, 20 were excluded after searching for duplicates. Afterwards, these 134 single records were meticulously scanned for compliance with our eligibility criteria. Finally, 16 met all the predefined inclusion criteria.[20-35] Of these studies, 3 were excluded from the quantitative analysis because their results could not be pooled in any of the prespecified comparisons,[33-35] so that 13 studies were included in the meta-analysis. Whenever it was possible, communication was established with the corresponding authors to retrieve more data from the published studies.

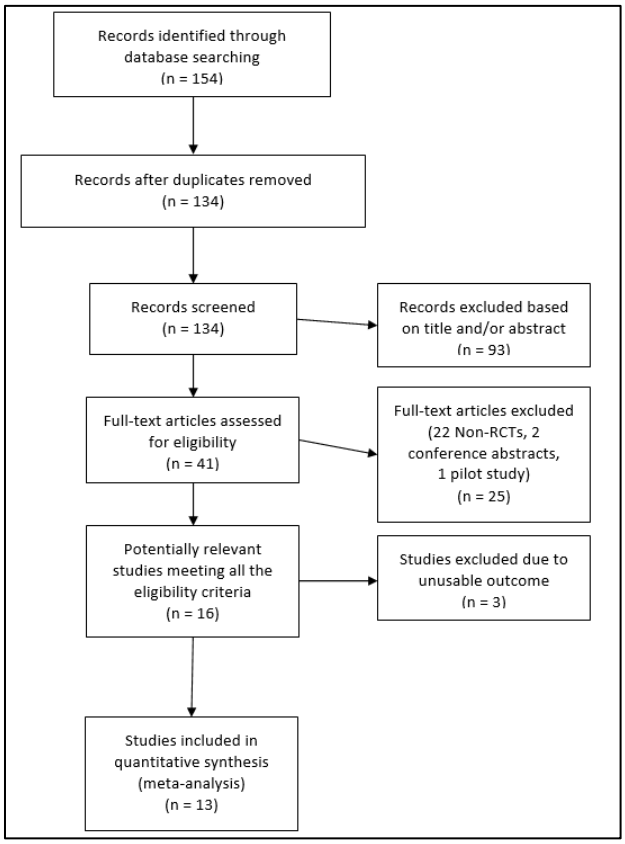


Table 1 Flow diagram of the literature search

Studies characteristics and Methodological quality assessment

There are 5 studies comparing pre-operative IVB versus sham injection,[20, 22, 23, 28, 31] and 8 studies comparing pre-operative IVB versus no treatment.[21, 24-27, 29, 30, 32] All studies, except for one, included patients suffering not only from non-clearing VH but also from TRD. The only exception was the study of Faisal et al. that analyzed patients suffering exclusively from VH.[25] In one study, there are two different time frames examined for pre-operative IVB administration.[23] These two groups were combined in the present study in order to avoid double counting bias.[36] Moreover, in two studies IVB was used in concentrations different from the standard 1.25/0.05ml.[28, 29] Details on number of subjects enrolled, indication for vitrectomy, intervention groups and outcomes measured are presented in Table 2.

STUDY	CASES	INDICATION FOR VITRECTOMY	INTERVENTION GROUPS	OUTCOMES MEASURED
Ahmadieh 2009	68	Non-clearing VH, TRD, active or progressive PDR	• IVB 1.25mg – 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 1.25mg – 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 1.25mg – 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	• Intraoperative bleeding • Endodiathermy

			• IVB 1.25mg – 3 weeks pre-op • Sham – 3 weeks pre-op	• Iatrogenic retinal break • Relaxing Retinotomy • Operation Time • Post-op VH
El-Batarny 2008	30	VH, TRD	• IVB 1.25mg – 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 1.25mg – 7 days pre-op • No IVB	• Surgical time • Iatrogenic retinal break • Intraoperative bleeding
Farahvash 2011	35	VH, TRD	• IVB 1.25mg – 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 1.25mg – 2 days pre-op • No IVB	• Operation time • Intraoperative bleeding • Ocular Hypertension • RD • Neovascular glaucoma (NVG) • Post-op VH • Retinotomies
Manabe 2015	66	Non-clearing VH, TRD	• IVB 0.16mg – 1 day pre-op • Sham – 1 day pre-op	• VEGF in vitreous • Endodiathermy

				• Iatrogenic retinal breaks • Endotamponade • Operational time • Post-op VH • Elevation of IOP • NVG • BCVA • Second Vitrectomy • Adverse events
Modarres 2009	40	TRD	• IVB 2.5mg – 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 1.25mg – 5-7 days pre-op • No IVB	• Operation time • Intraoperative bleeding • Endodiathermy • Intraoperative retinal breaks • Post-op anatomic attachment
Sohn 2012	20	TRD, combined tractional and rhegmatogenous RD	• IVB 1.25mg – 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 1.25mg – 1 week • No IVB	• BCVA • Post-op VH • Rubeosis iridis • Hyphaema

Table 2 Studies Characteristics

The quality of the studies included has been assessed by using the RoB Cochrane tool for Systematic Reviews of interventions and it is presented in Figure 1.

Figure 1 RoB assessment

A. Analysis per operation time

Eight studies with a total of 540 patients provided data for the comparison of total operation time. The overall pooled difference between the examined study groups after synthesizing the outcomes of the included studies revealed decreased total operation time with IVB [RE MD=-20.22, 95% CI = (-26.25, -14.19), P_Q=0.004, I^2=66% (Figure 2)].

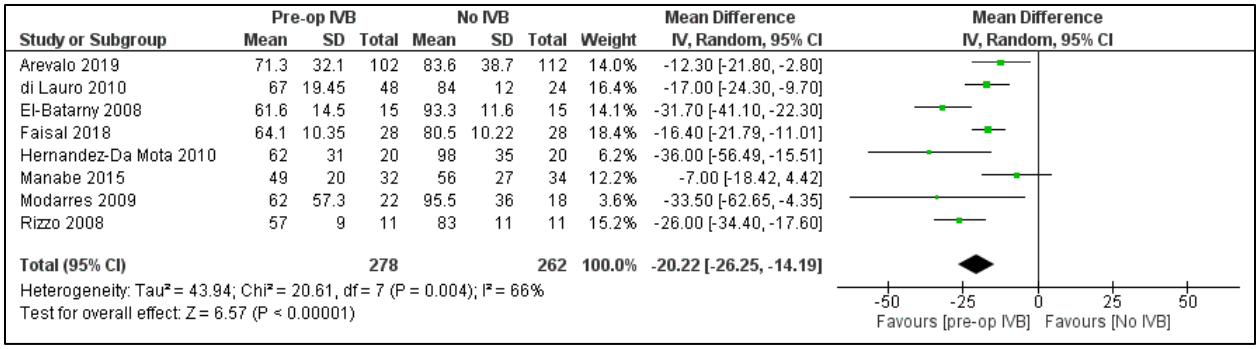


Figure 2 Analysis per operation time

The studies included in this analysis showed significant heterogeneity, thus RE model was used. In order to explore this heterogeneity, subgroup analysis has been performed. Studies including patients who received IVB less than 5 days pre-operatively and studies including patients who received IVB 5-21 days pre-operatively were analyzed separately. The beneficial effect of pre-operative IVB remained statistically significant in all comparisons (Figures 3 and 4).

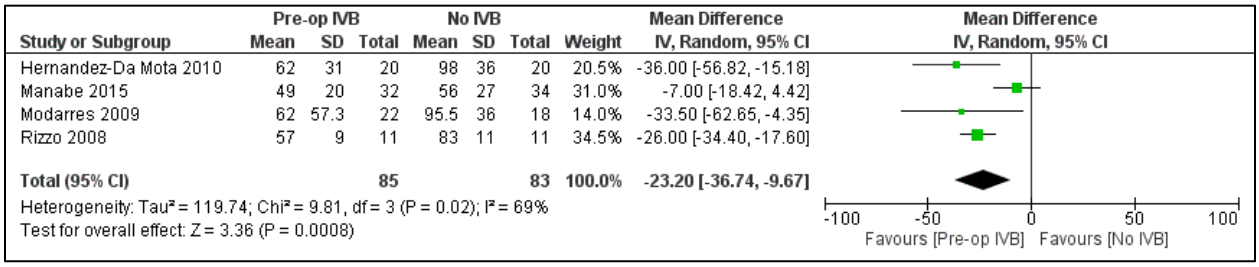


Figure 3 Analysis per operation time in studies administering IVB less than 5 days pre-op

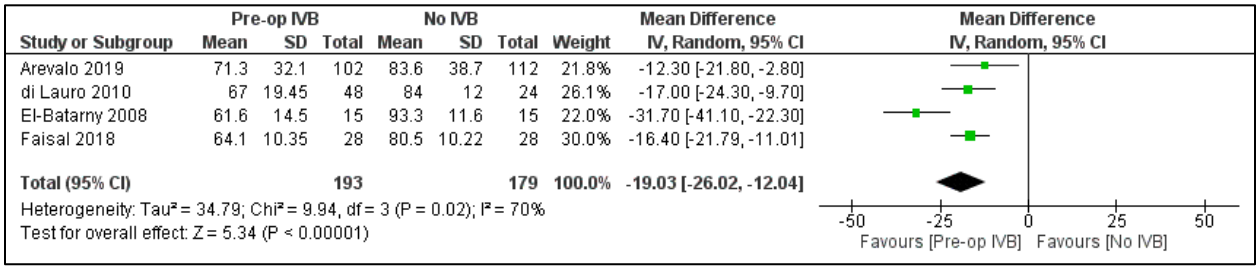


Figure 4 Analysis per operation time in studies administering IVB 5-21 days pre-op

Moreover, a meta-regression model including number of surgeons performing the operations (p=0.30>0.05), the performance of delamination during surgery (p=0.421>0.05), the performance of combined phacovitrectomy vs. vitrectomy alone (p=0.26>0.05) and the mean age of patients (p=0.57>0.05) showed no statistically significant difference for the aforementioned factors.

Thus, it can be assumed that the heterogeneity may be due to the different experience and skills of surgeons among studies or may have to do with the surgical equipment, the complexity of cases and the way surgical time was measured. However, the fact that the same prespecified surgeons performed the operations in each study separately suggests that our findings are robust.

B. Analysis per iatrogenic intraoperative retinal break

In order to compare the occurrence of iatrogenic intraoperative retinal breaks, data from 6 studies, including 498 individuals, were synthesized. The pre-operative administration of IVB was associated with significantly less breaks [FE OR=0.37, 95% CI = (0.24, 0.58), P_Q=0.22, I^2=29% (Figure 5)].

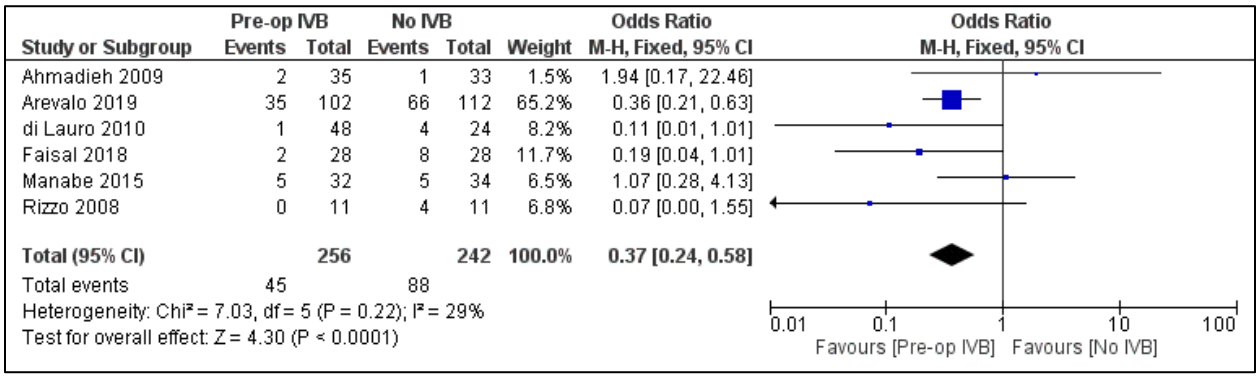


Figure 5 Analysis per iatrogenic intraoperative retinal break

C. Analysis per logMAR BCVA at the last follow-up visit

Regarding the comparison of logMAR BCVA prognosis between groups treated with pre-operative IVB and patients not receiving pre-operative IVB, data from 6 studies including 440 subjects were synthesized. A statistically significant better long-term BCVA

was found in the groups treated with pre-operative IVB [FE MD=-0.13, 95% CI = (-0.22, -0.04), P_Q=0.37, I^2=7% (Figure 6)].

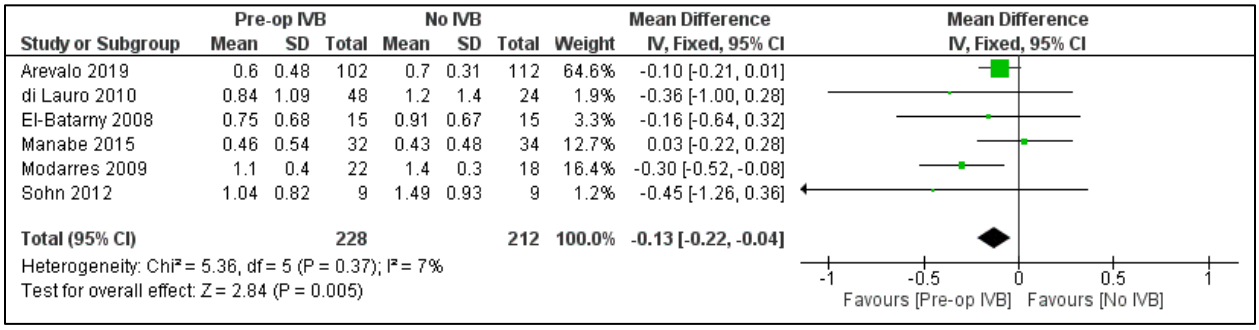


Figure 6 Analysis per logMAR BCVA at the last follow-up visit

In order to examine whether the analysis of different time frames post-operatively and the inclusion of patients with different baseline logMAR BCVA has introduced any heterogeneity in this data synthesis, a meta-regression model was developed. Both the time of last follow-up visit (p=0.55>0.05) and the baseline logMAR BCVA (p=0.26>0.05) were not found statistically significant. When controlling for combined phacovitrectomy as a confounder, a sensitivity analysis by excluding the only study (El-Batarny et al.[24]) that reported the performance of combined surgery provided statistically significant results. (see Appendix)

D. Analysis per presence of post-operative VH

Data from 9 studies examining 654 patients were synthesized in this comparison. The administration of pre-operative IVB was associated with statistically significantly less post-operative VHs [RE OR=0.21, 95% CI = (0.11, 0.40), P_Q=0.03, I^2=53% (Figure 7)].

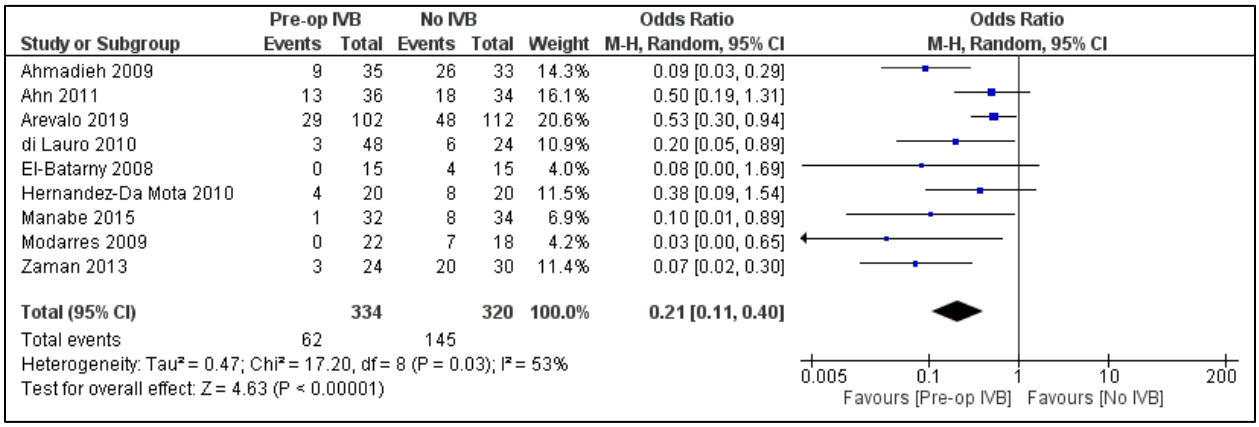


Figure 7 Analysis per presence of post-operative VH

The meta-regression model which analyzed total follow-up time (p=0.26>0.05) and mean age of patients (p=0.35>0.05) was not found statistically significant.

E. Analysis of the need for second vitrectomy

The need for second vitrectomy between groups was analyzed combining data from 8 studies including 568 subjects. The administration of pre-operative IVB was found to be associated with a lower risk of post-operative second vitrectomy of any cause [FE OR=0.34, 95% CI = (0.19, 0.59), P_Q=0.82, I^2=0% (Figure 8)].

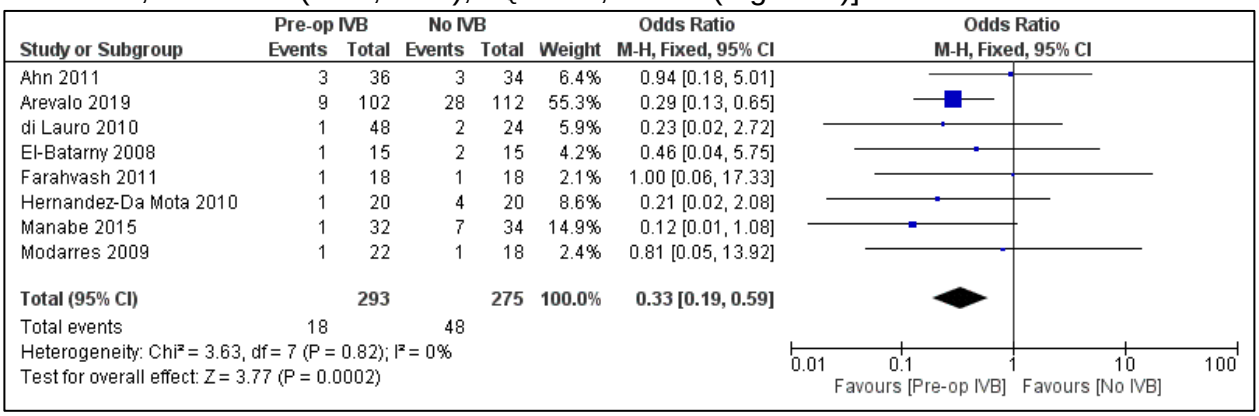


Figure 8 Analysis of the need for second vitrectomy

In order to increase the robustness of this comparison, we conducted subgroup analyses examining separately the need for second vitrectomy by cause. Pre-operative IVB proved to be of benefit for preventing second vitrectomy due to both RD [FE OR=0.44, 95% CI = (0.20, 0.96), P_Q=0.93, I^2=0%] and VH [FE OR=0.36, 95% CI = (0.16, 0.85), P_Q=0.46, I^2=0%] (Figures 9 and 10).

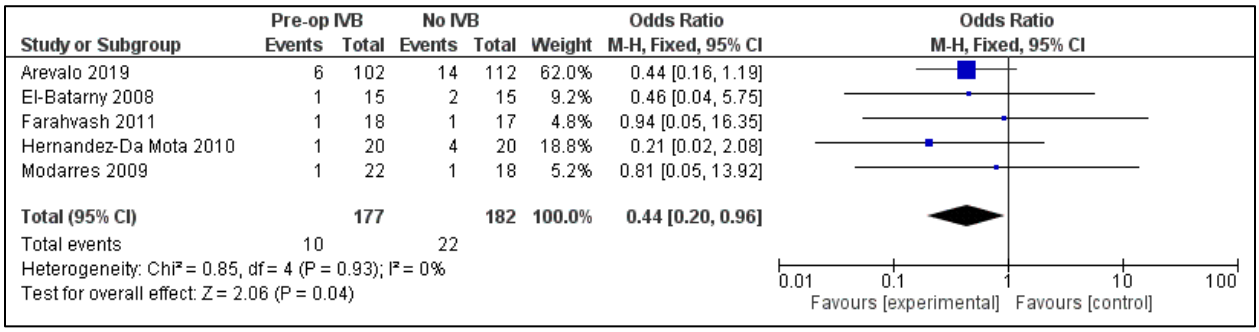


Figure 9 Analysis of the need for second vitrectomy due to RD

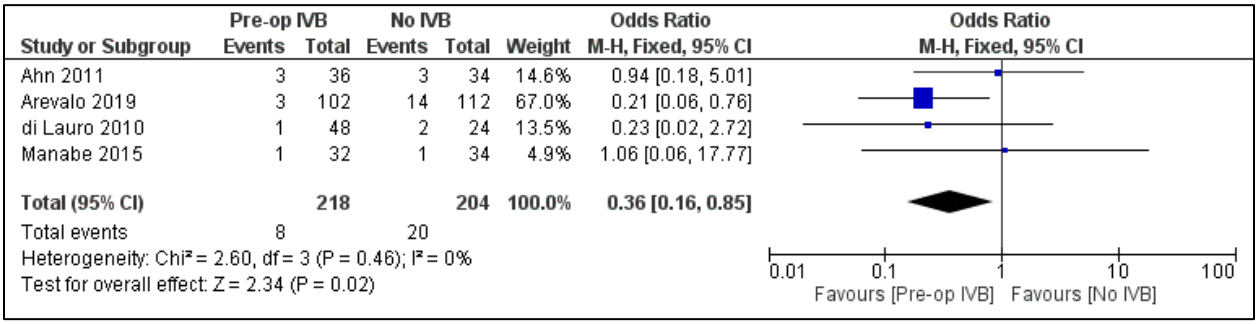


Figure 10 Analysis of the need for second vitrectomy due to VH

Sensitivity analyses

In order to improve the robustness of our findings, for every comparison done additional sensitivity analyses were performed according to the leave-one-out method. All of the comparisons proved to be statistically significant and in accordance with our initial findings (see Appendix for analytic details).

Publication bias

Publication bias was assessed for each comparison separately using funnel plots. All plots were symmetrical except for operation time. This asymmetry may be the result of the imbalance in surgeons' skills and different surgical equipment among studies (see Appendix for plots).

E. 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 the development of iatrogenic retinal breaks because of impaired retina view. Moreover, segmentation and delamination of fibrovascular membranes represents one of the most challenging vitreoretinal steps with increased risk or retinal tears or intraoperative bleeding. Intravitreal bevacizumab

preoperatively has been used off-label to improve surgical outcomes for these patients.[30] Our results suggest that a single pre-operative dose of IVB is associated with decreased mean surgical time and reduced number of iatrogenic retinal breaks. Additionally, patients pre-treated with IVB were shown to have statistically significant better BCVA at their last follow-up visit and fewer episodes of post-operative VHs. The reduction in post-operative VHs is probably due to the more efficient release of traction in these patients, since bevacizumab wears off post-operatively. Also, the need for second vitrectomy for any cause was statistically significant smaller. These findings are of great value providing evidence for the use by vitreoretinal surgeons of a very useful tool that may facilitate the management of these challenging cases, which in their vast majority belong to the working population. Vision loss in this group of patients can have a series of negative personal and social consequences.[37]

The first documented use of pre-operative IVB in diabetic vitrectomy was by Chen et al. who administered a single IVB in a 27 year old patient reporting promising results.[38] Since then, many studies have been conducted to test the effects of pre-operative IVB in patients undergoing diabetic vitrectomy.

Regarding the effect of pre-operative IVB on surgical procedure, Yeh et al. conducted a comparative case-control study where they alternately assigned diabetic patients requiring vitrectomy either to a single IVB injection 1 week before surgery or no pre-operative IVB.[39] They concluded that IVB reduces intraoperative bleeding and helps in quicker anatomic success. However, it cannot control recurrent hemorrhage and it may increase vitreoretinal traction. These findings are in accordance with the study of Oshima et al., who reported shorter surgical time and less intraoperative bleeding when comparing IVB prior to microincision vitrectomy (25-g and 23-g) surgery versus conventional (20-g) vitrectomy.[40] The reduction of intra-operative bleeding was also postulated by an institutional study measuring the number of erythrocytes in the fluid retrieved from the vitrectomy cassette in people treated with IVB prior to vitrectomy.[33]

Considering the post-operative outcomes of a single pre-operative IVB, a retrospective chart review performed by Gupta et al. as part of the Diabetic Retinopathy In Various Ethnic Groups (DRIVE-UK) study reported that patients treated with IVB prior

to vitrectomy had better long-term BCVA and developed statistically significantly less post-operative VH.[41] In a subgroup analysis of the DRIVE-UK study, pre-operative IVB was found to have a protective effect on the development of diabetic macular edema post-operatively at 12 months follow-up.[42] Pokroy et al. suggested that pre-operative IVB is particularly advantageous in young patients regarding BCVA improvement and surgical time reduction.[43] The reduction of post-operative VH has been analyzed in many observational studies as well.[44, 45] In a retrospective chart review, Lo et al. raised concerns about the favorable results of pre-operative IVB in post-operative VH.[46] Nevertheless, the two groups analyzed were quite heterogenous regarding age and surgical technique used. Moreover, Yang et al. suggested that pre-operative IVB resulted in faster vitreous clear up postoperatively in eyes undergoing diabetic vitrectomy with C_3F_8 tamponade.[47] Regarding the need for repeat PPV, Hu et al. suggested that IVB prior to vitrectomy might reduce the rate of reoperation in patients with VH alone, but they found a higher rate of second vitrectomy in IVB patients with combined VH and TRD.[48] Lastly, the beneficial effect of pre-operative IVB has been reported in East-African patients as well.[49]

In order 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.[50] 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 in agreement with our subgroup analyses.

Regarding the required dose of IVB in order to provide its beneficial effect, Hattori et al. reported that 0.16mg dose was as effective as 1.25mg in terms of reducing intraoperative bleeding.[51]

The benefits of pre-operative IVB have been also demonstrated at molecular level. By analyzing neovascular membranes from subjects undergoing diabetic vitrectomy, Han et al. concluded that patients pre-treated with IVB had statistically significant less vascular endothelial cells, expression of VEGF and hypoxia inducible factor-1a.[34] Furthermore, the reduction of vitreous VEGF levels has been shown by Sohn et al.[31]

A Cochrane review by Smith et al. highlighted the beneficial effect of a single pre-operative IVB injection in reducing early post-operative VH and post-operative RD,

however the inclusion of a retracted paper might have influenced the results.[52] Two previous meta-analyses support the adjunctive use of pre-operative IVB in diabetic vitrectomy.[53, 54] However, according to authors, the small number of studies included could not provide robust conclusions, there were concerns about possible publication bias and methodological flaws while the publication of more studies with larger sample size recently provided additional evidence which is worthwhile reviewing systemically.

The present meta-analysis has several limitations in terms of included data. First of all, the majority of the studies included analyze small samples (<100 subjects), thus reducing their statistical power. Moreover, there is some diversity among studies about the indication for diabetic vitrectomy and the type of PPV used. Furthermore, for this meta-analysis only three electronic databases were searched to retrieve relevant studies. However, by including PubMed and Cochrane, hardly any high-quality published study was overlooked. Different follow-up times in each study were adjusted by conducting additional meta-regression analyses. Regarding the quality of individual studies included in the present meta-analysis, there is only a minor disparity. While Arevalo et al. conducted a study with sufficient sample size, the multi-center nature of their research induces a diversity in surgical techniques and equipment used.[22] The double-masked RCT of Ahmadieh et al. has a big drop-out rate from the calculated sample size, thus not establishing significant statistical power.[20] The lack of a pre-specified analysis plan of the data combined with the execution of multiple analyses in the studies of Zaman et al., Hernandez-Da Mota et al. and Farahvash et al. makes them suspect for selective report of the outcome.[26, 27, 32] In the study of Di Lauro et al., baseline differences among treatment groups may influence the results.[23] The lack of sham injection, small baseline differences between groups and no double-masking might affect the results in the study of Ahn et al.[21] The large range of follow-up times combined with lack of masking may predispose to bias in the study of El-Batarny et al.[24] The main sources of bias in the study of Rizzo et al. is the relatively small sample size and the limited follow-up time.[30] Limited follow-up time was also an issue in the study of Manabe et al.[28] Possible yet unavoidable lack of masking together with a questionable classification system for fibrovascular proliferation in PDR are the main issues in the study of Modarres et al.[29] Lack of masking

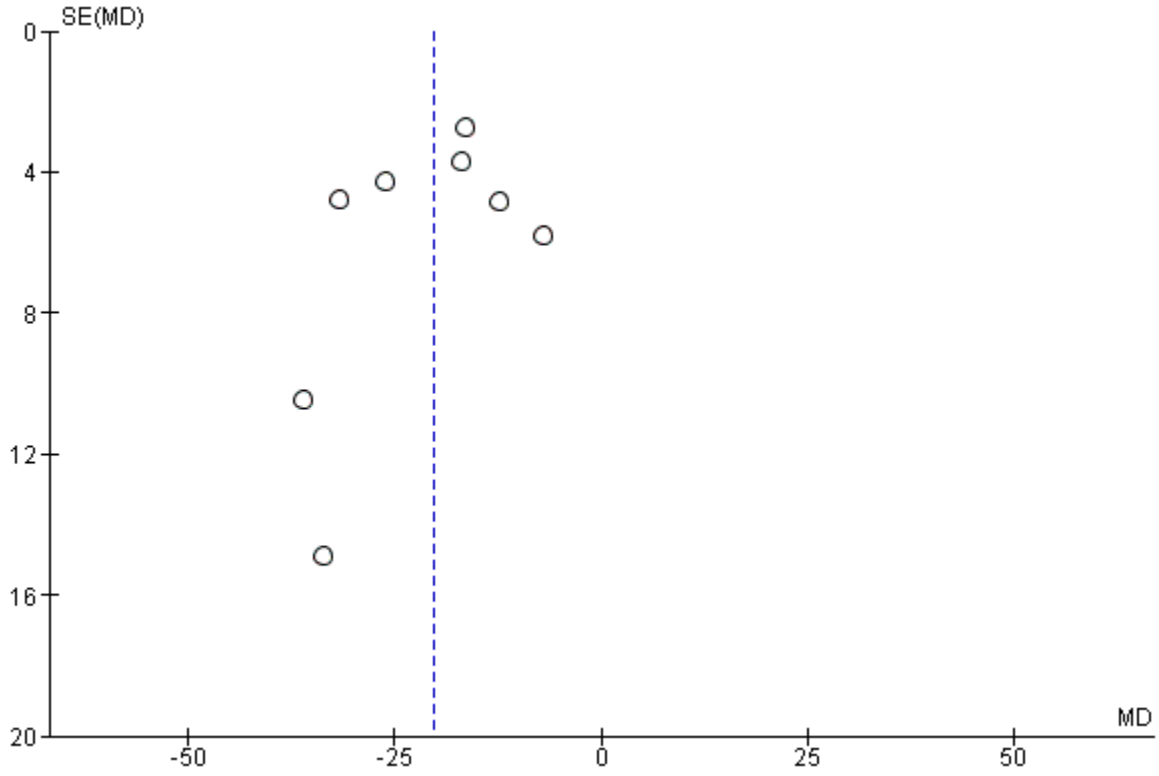
is also a limitation in the study of Faisal et al.[25] Finally, the very small sample size in the study of Sohn et al. reduces its statistical power.[31]

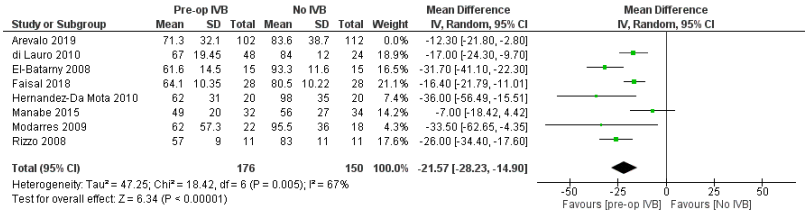
To the best of our knowledge the present study is the most comprehensive meta-analysis performed assessing pre-operative use of IVB in patients undergoing diabetic vitrectomy, having included all the recent trials published on this issue. The thorough sensitivity and subgroup analyses are strengths of our study supporting the robustness of our results.

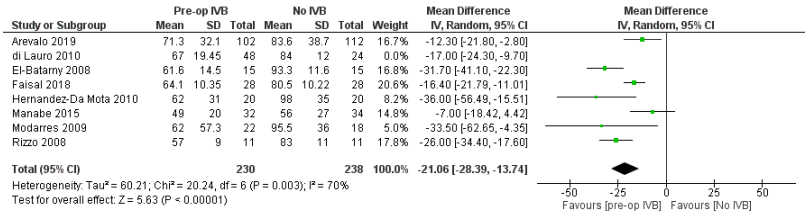
In conclusion, based on the current evidence, the adjunctive use of pre-operative bevacizumab in patients undergoing vitrectomy for PDR is quite beneficial as it improves the feasibility of the operation by reducing the surgical time and the incidence of iatrogenic retinal breaks; it also provides patients with better visual prognosis and less post-operative VHs. Moreover, our results support the protective role of pre-operative IVB against the need for second vitrectomy. Studies comparing different treatment doses and times for the pre-operative administration of IVB are necessary to further investigate this issue.

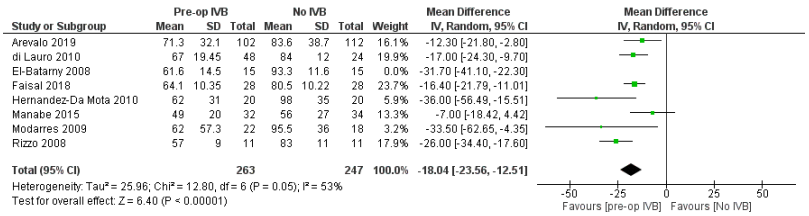
Appendix – Funnel plots and sensitivity analyses

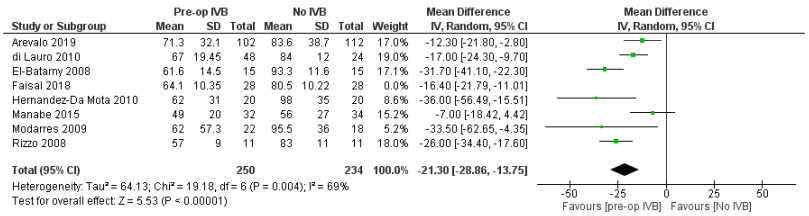
A. Operation Time

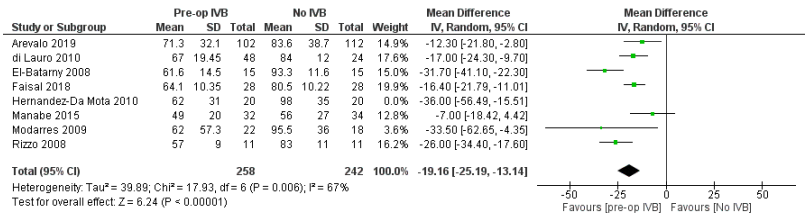


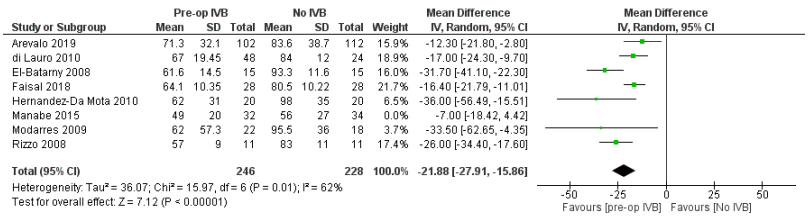


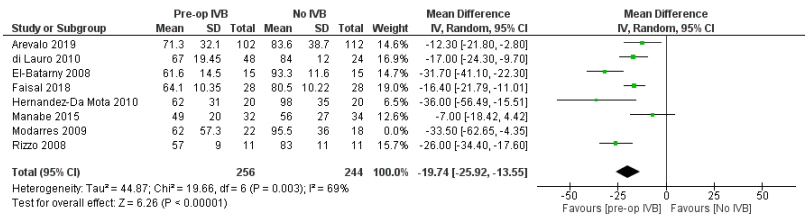


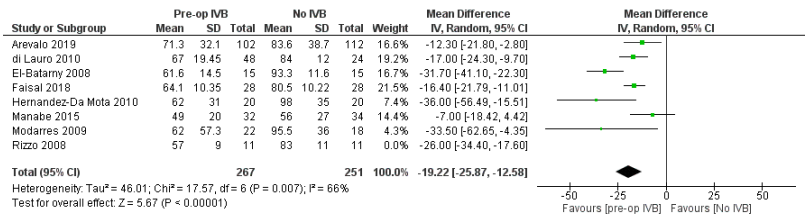




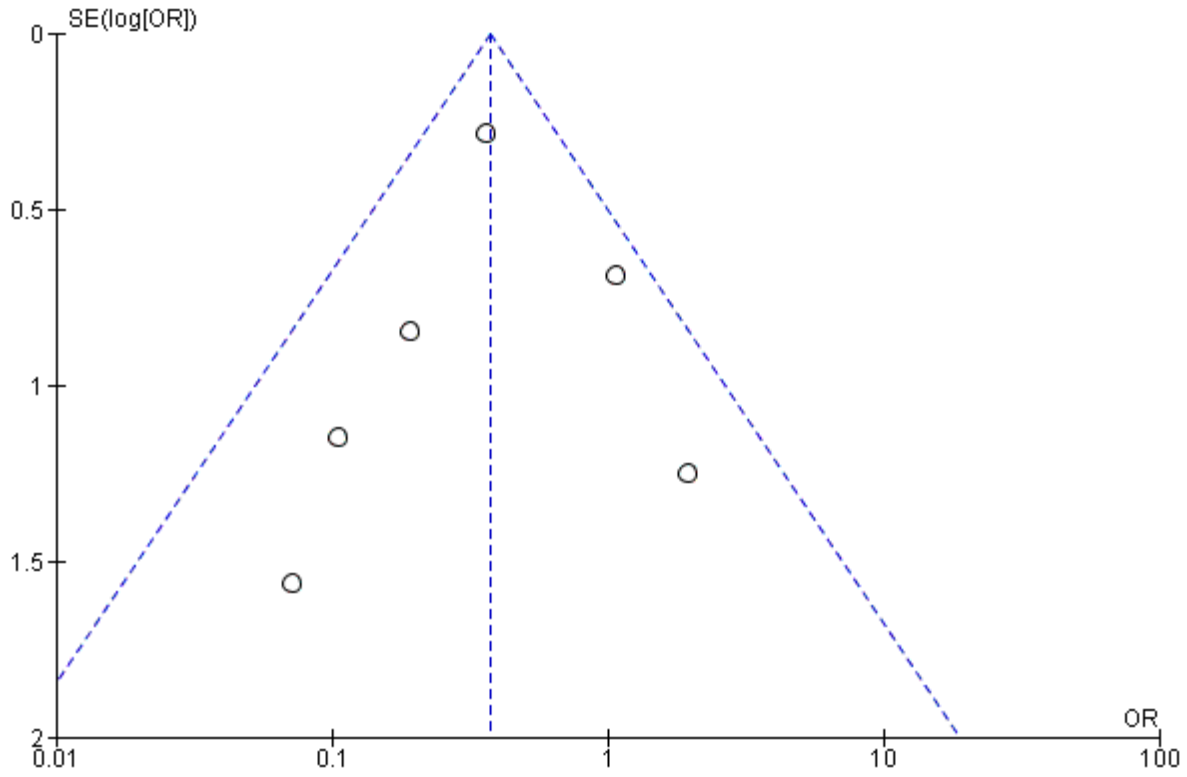


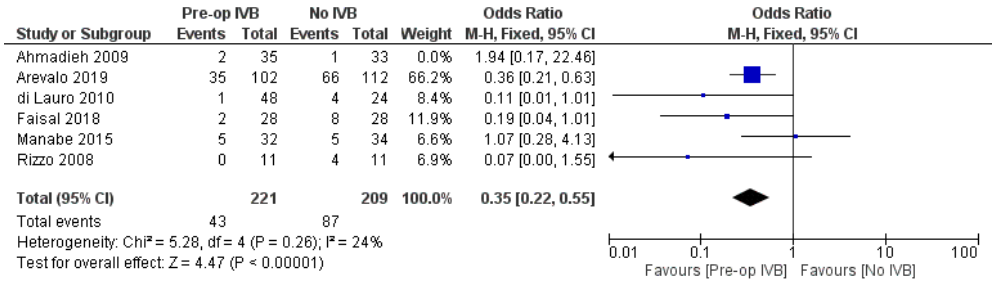


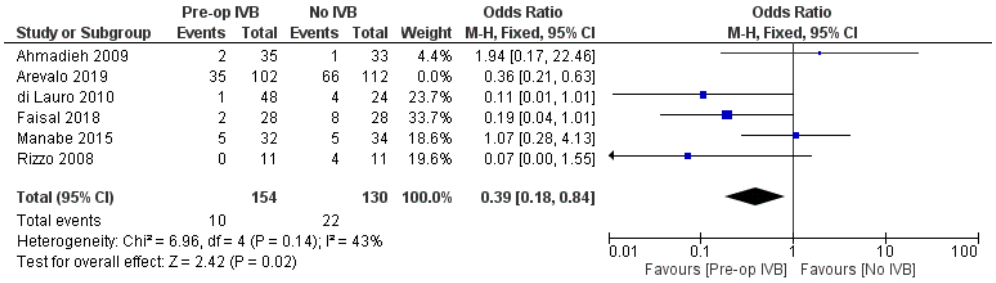


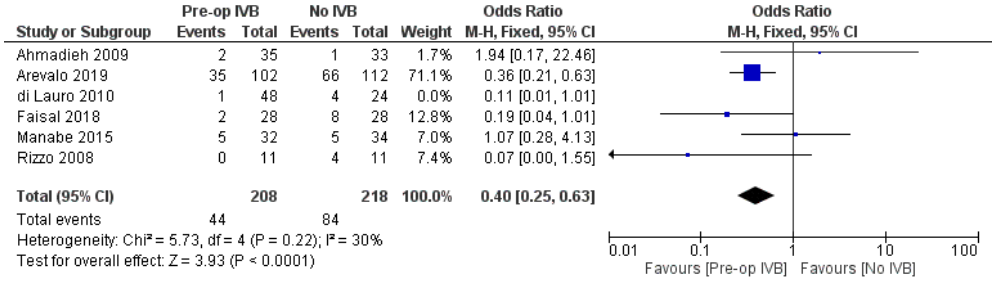


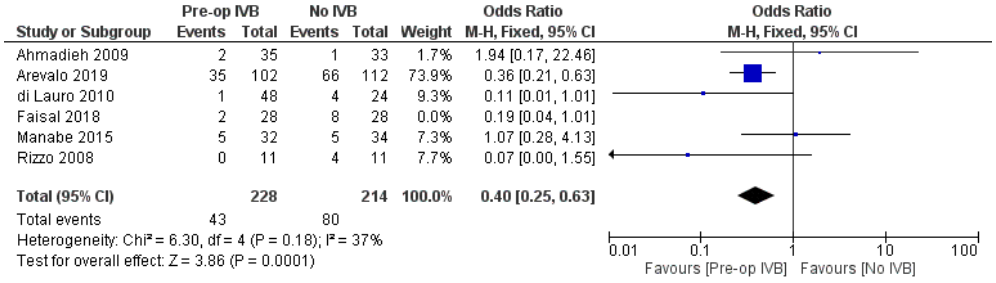
B. Intraoperative iatrogenic retinal breaks

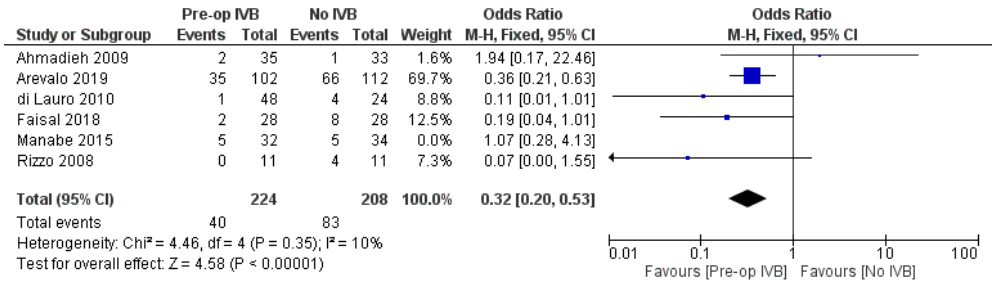


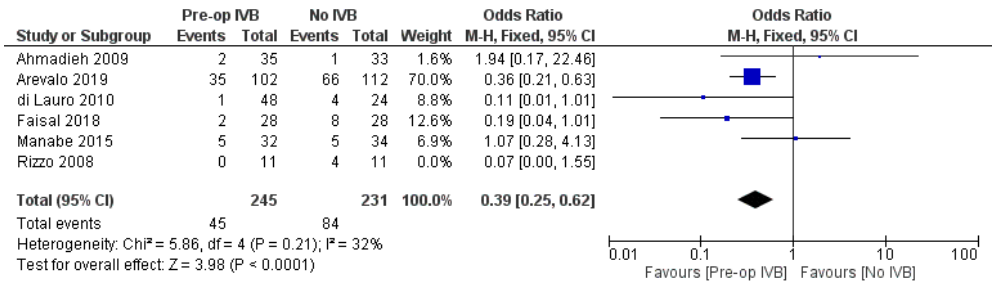




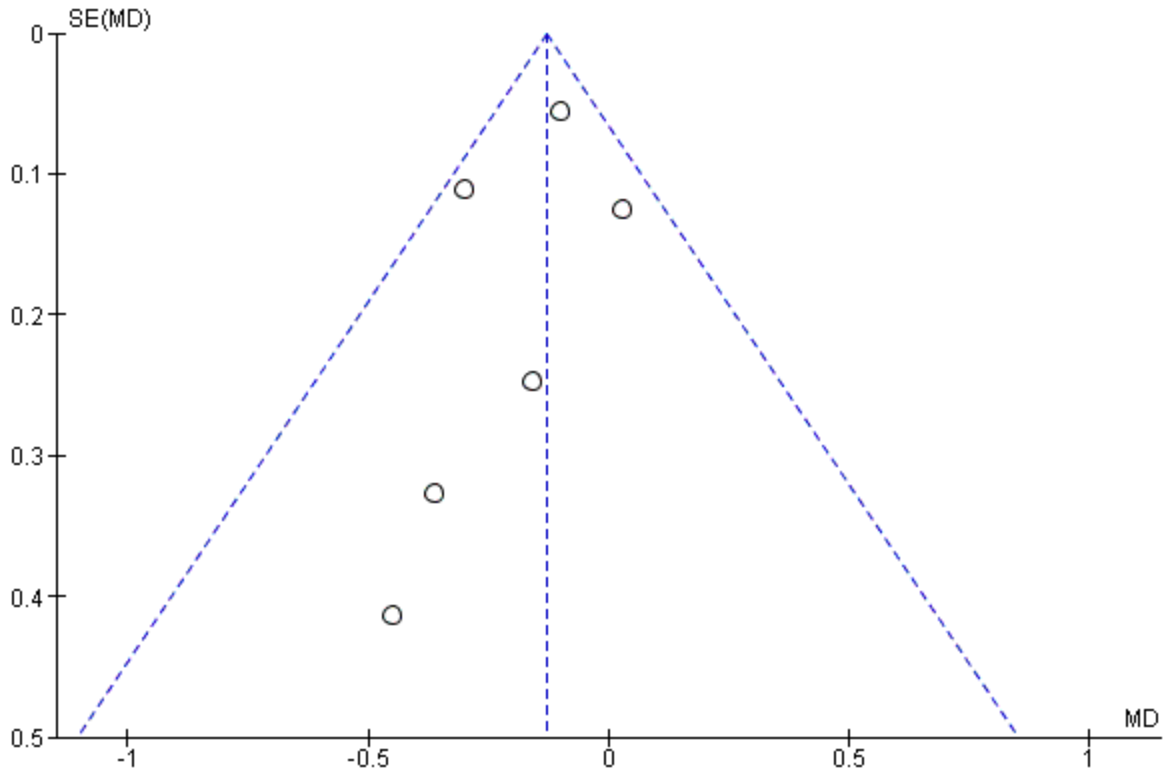


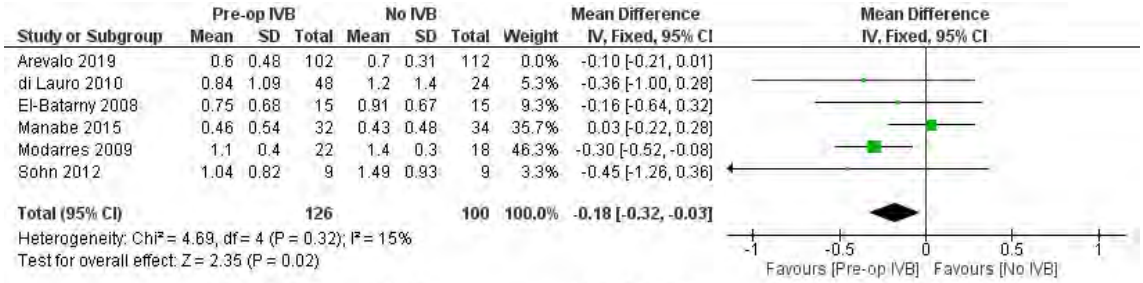


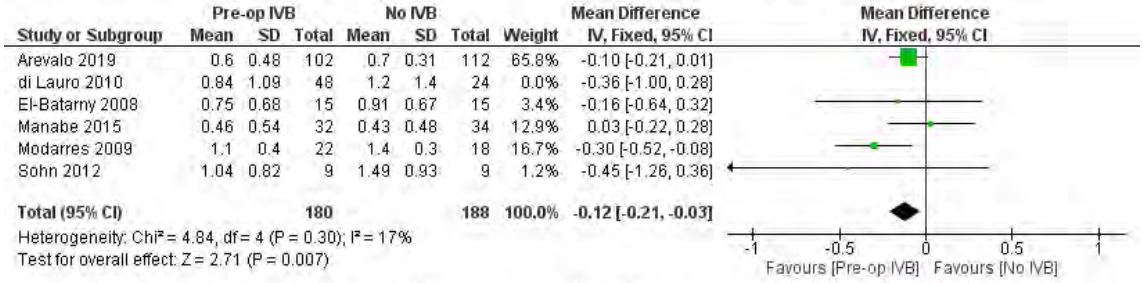


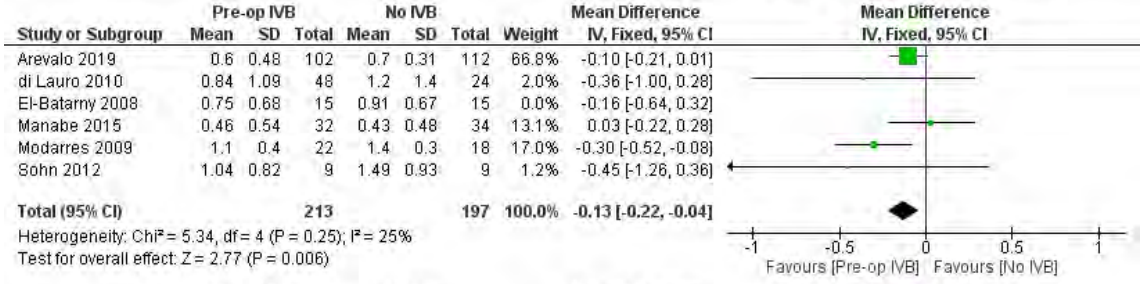


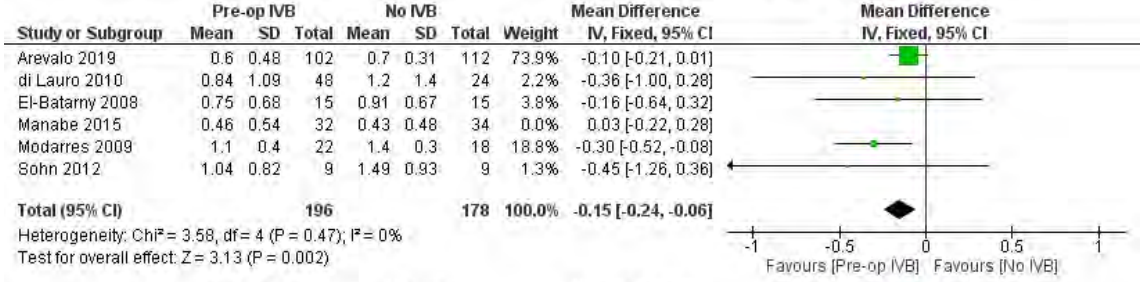
C. LogMAR BCVA at last follow up

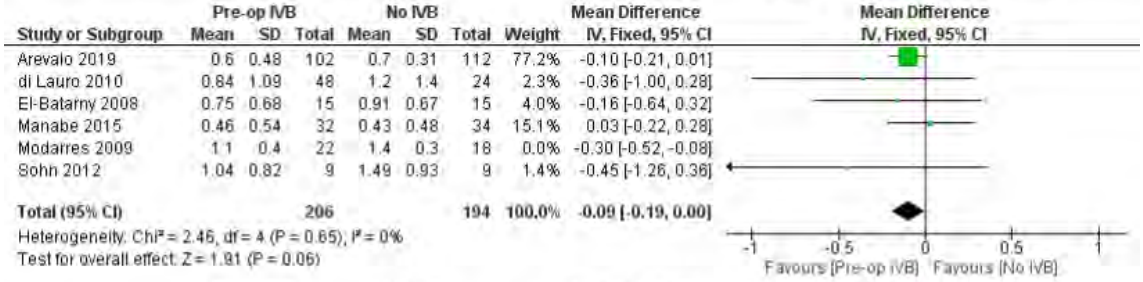


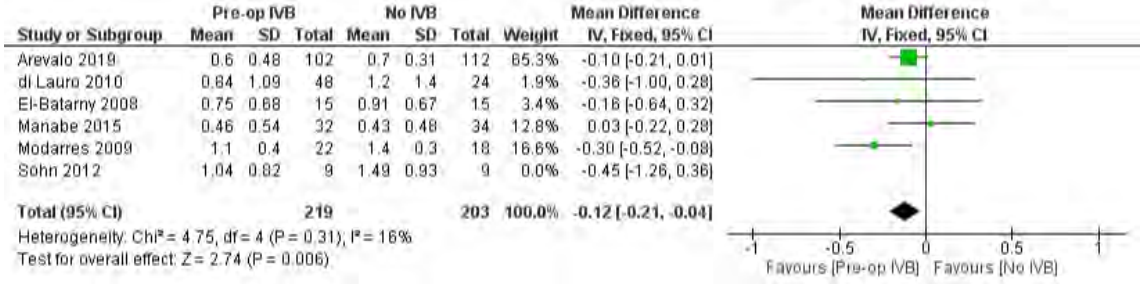




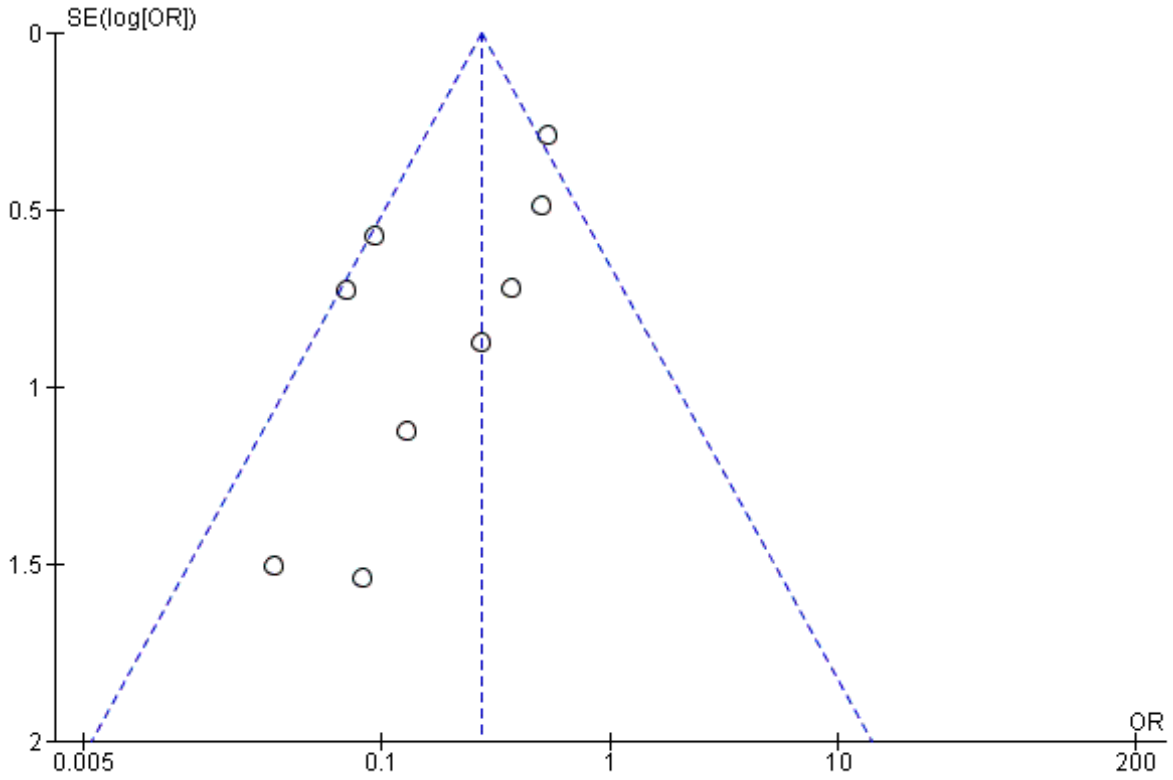


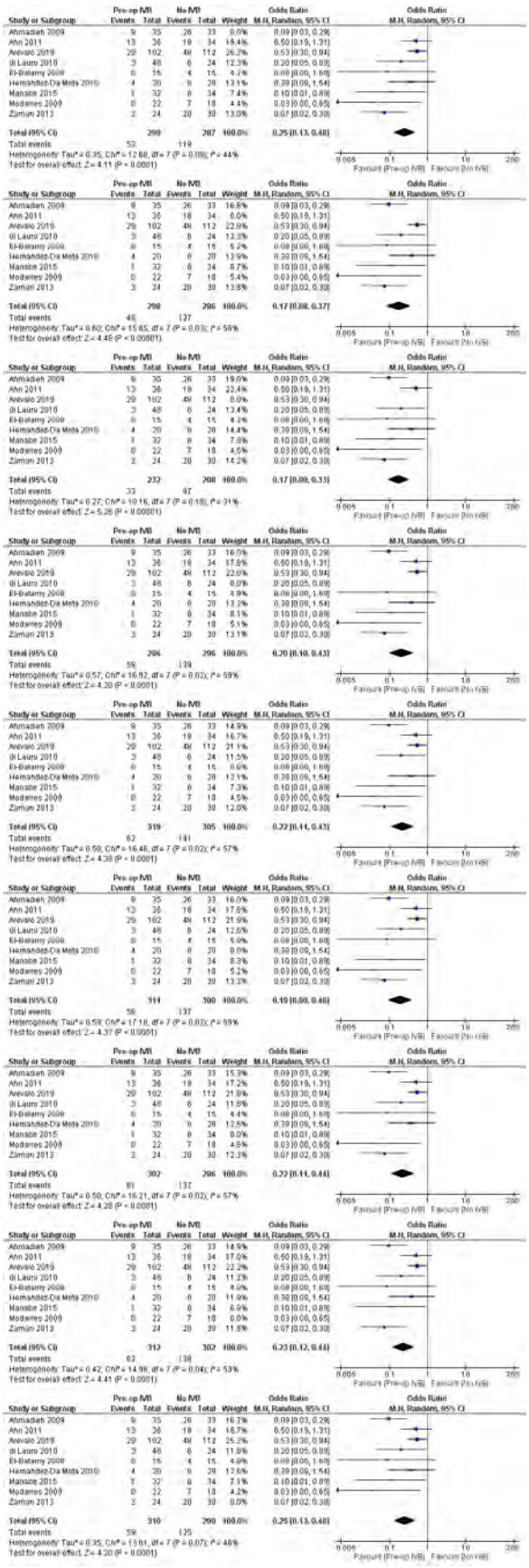




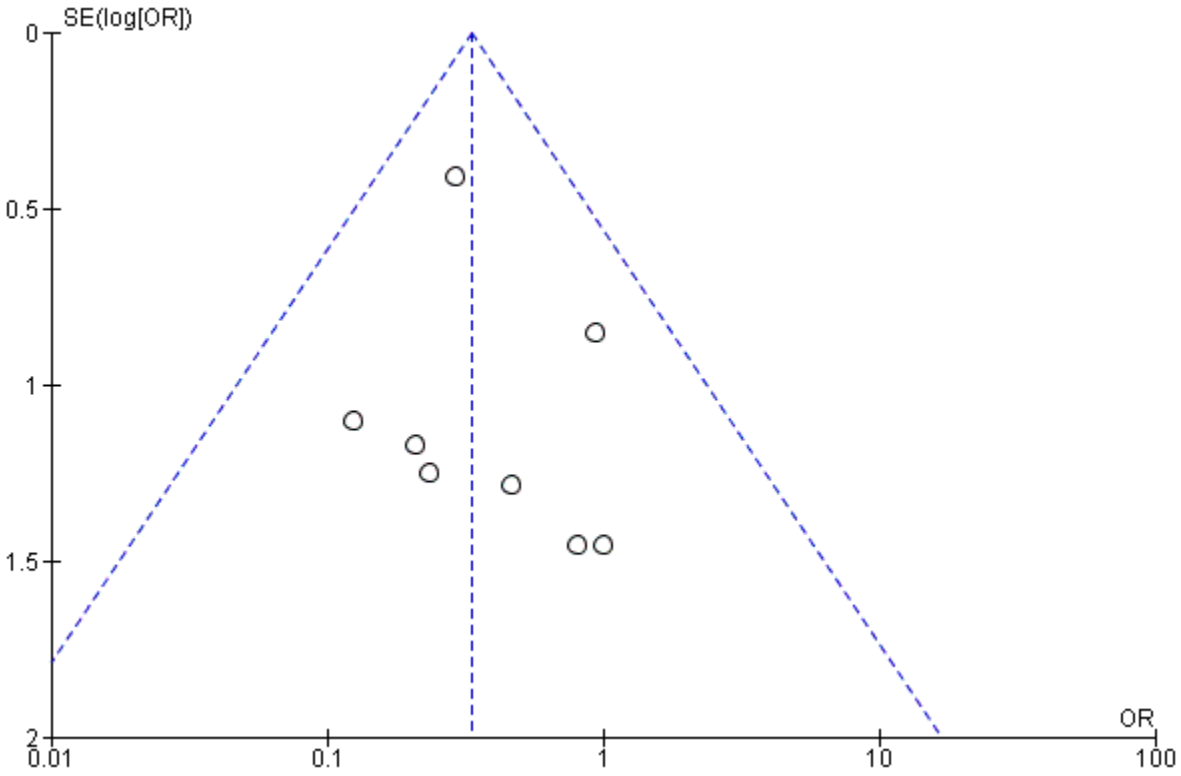


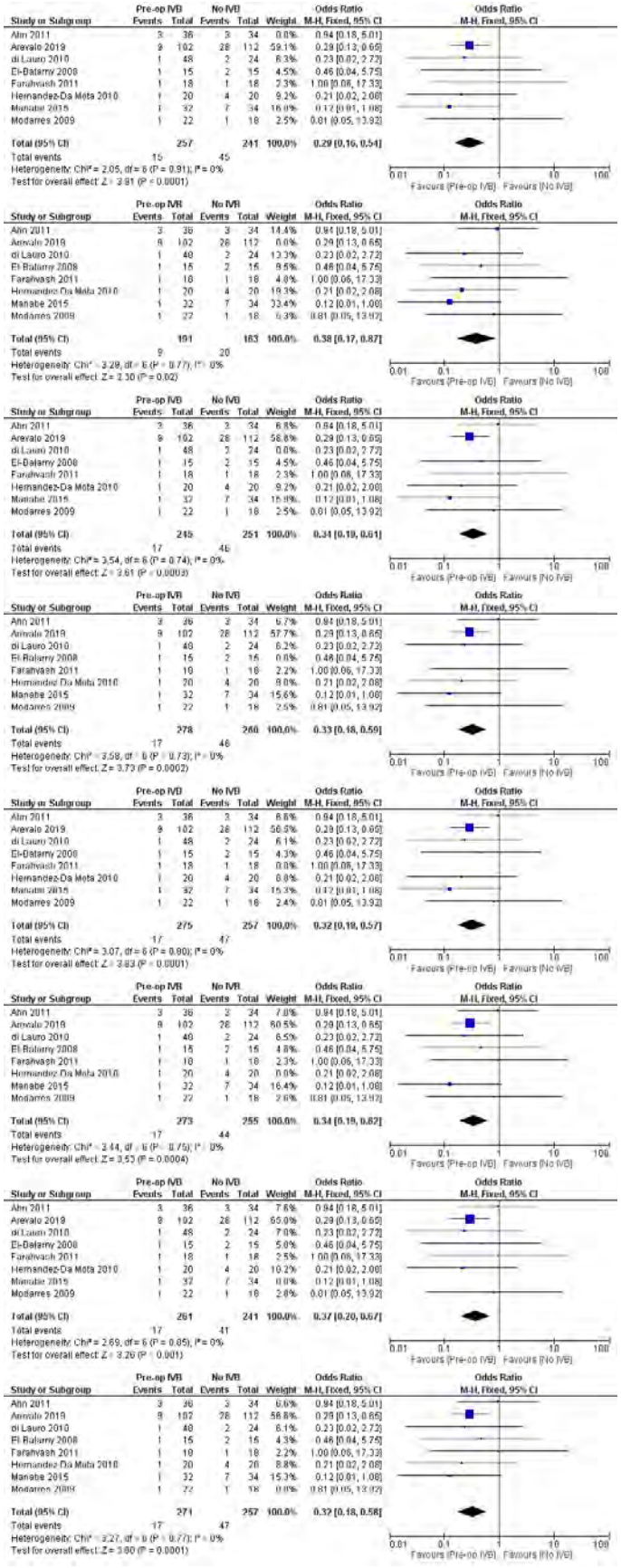
D. Post-operative VH





E. Second Vitrectomy





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