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Preoperative Anti-VEGF for Vitrectomy in Proliferative Diabetic Retinopathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 March 2025 and was last updated on 28 May 2025.

INTRODUCTION

Review question / Objective Does the preoperative use of monoclonal antibodies against vascular endothelial growth factor in clinical trials improve clinical outcomes and reduce complications in patients with proliferative diabetic retinopathy undergoing vitrectomy, compared to vitrectomy alone?

Rationale Proliferative diabetic retinopathy (PDR) is one of the leading causes of blindness in patients with diabetes mellitus. In advanced cases, vitrectomy is the standard surgical treatment to remove fibrovascular tissue and improve visual function. However, this procedure can be associated with intraoperative and postoperative complications, such as vitreous hemorrhage, recurrent fibrosis, and retinal detachment, which may affect surgical outcomes and visual recovery.

Monoclonal antibodies against vascular endothelial growth factor (VEGF) have been proposed as a preoperative treatment to reduce intraoperative bleeding and improve surgical visualization. Several clinical studies suggest that preoperative anti-VEGF therapy may facilitate surgery and decrease complications. However, the evidence remains inconclusive, and the potential benefits compared to vitrectomy alone have not been fully established.

This study aims to evaluate whether the preoperative use of anti-VEGF monoclonal antibodies improves clinical outcomes and reduces complications in patients with proliferative diabetic retinopathy undergoing vitrectomy, compared to vitrectomy alone. The results of this research could provide valuable insights for optimizing the surgical management of PDR and improving patient outcomes.

Condition being studied Proliferative diabetic retinopathy requiring vitrectomy as a surgical intervention.

METHODS

Search strategy Two researchers independently conducted the systematic review in a blinded manner, without knowing each other's decisions. For the systematic search, they consulted the PubMed, ClinicalTrials.gov, and Cochrane Central databases, using the following search strategy based on Boolean strings:

("Diabetic Retinopathy" AND "Vitrectomy" AND "Anti-VEGF")
("Diabetic Retinopathy" AND "Vitrectomy" AND "Bevacizumab")
("Diabetic Retinopathy" AND "Vitrectomy" AND "Ranibizumab")
("Diabetic Retinopathy" AND "Vitrectomy" AND "Aflibercept")
("Diabetic Retinopathy" AND "Vitrectomy" AND "Preoperative Anti-VEGF")
("Diabetic Retinopathy" AND "Vitrectomy" AND "Preoperative Bevacizumab")
("Diabetic Retinopathy" AND "Vitrectomy" AND "Preoperative Ranibizumab")
("Diabetic Retinopathy" AND "Vitrectomy" AND "Preoperative Aflibercept")
("Proliferative Diabetic Retinopathy" AND "Vitrectomy" AND "Preoperative Anti-VEGF")
("Proliferative Diabetic Retinopathy" AND "Vitrectomy" AND "Preoperative Bevacizumab")
("Proliferative Diabetic Retinopathy" AND "Vitrectomy" AND "Preoperative Ranibizumab")
("Proliferative Diabetic Retinopathy" AND "Vitrectomy" AND "Preoperative Aflibercept").

Participant or population We will include both male and female patients of any nationality with proliferative diabetic retinopathy who require vitrectomy as a surgical treatment, comparing outcomes between those who receive a preoperative monoclonal antibody targeting vascular endothelial growth factor and those who undergo vitrectomy alone.

Intervention Any preoperative monoclonal antibody targeting vascular endothelial growth factor for vitrectomy in proliferative diabetic retinopathy.

Comparator Vitrectomy for proliferative diabetic retinopathy without preoperative monoclonal antibody targeting vascular endothelial growth factor.

Study designs to be included Clinical studies with an experimental design will be included, specifically randomized controlled trials (RCTs) with a parallel intervention design, regardless of the blinding method used.

Eligibility criteria
1.Inclusion criteria: Articles published in peer-reviewed scientific journals in English between January 2005 and January 2025 will be included. Eligible studies must be experimental in design (randomized controlled trials) and directly compare the preoperative use of monoclonal antibodies targeting vascular endothelial growth factor with the absence of such treatment in patients with proliferative diabetic retinopathy requiring vitrectomy. Additionally, studies must have a minimum sample size of 10 patients. 2. Exclusion Criteria: We will exclude studies such as brief comments, letters to the editor, literature reviews, systematic reviews (with or without meta-analysis), and those that compare the pre-vitrectomy use of monoclonal antibodies targeting vascular endothelial growth factor in combination with one or more other medications as an intervention.

Information sources The databases to be consulted include PubMed, Cochrane CENTRAL, and the ClinicalTrials.gov registry.

Main outcome(s) The primary outcome variables to be evaluated will include the overall surgical outcome (success rate, failure rate, and pre- vs. post-treatment measures), all reported intraoperative and postoperative complications, as well as procedural characteristics such as surgical time and other relevant factors. These outcomes will be analyzed using appropriate statistical methods based on the findings of the systematic review, which may include mean differences, analysis of binary outcome variables (e.g., relative risk or odds ratio), depending on the nature of the data obtained.

Additional outcome(s) The secondary outcome variables will include both study-level and population-level data. Study-level data will include details such as authorship, publication year, country of origin, number of study centers, sample size, blinding method, intervention model (number of arms analyzed in parallel), type of monoclonal antibody used, intervention dosage, route of administration, and follow-up duration. Population-level data will include baseline demographic characteristics (e.g., patient age, pre-existing conditions, and comorbidities), along with any other relevant patient-level information.

When essential data were missing from the original manuscript, the study authors were contacted to request the missing information. If this approach was unsuccessful, standardized mathematical methods recommended in the literature were applied. If neither strategy provided the necessary data, the study was excluded from the systematic review.

Data management After the database search, all retrieved articles will be imported into a reference manager, specifically Zotero v6.0.37 (Digital Scholar, VA, USA). Duplicate records will be identified and removed. The remaining studies will be evaluated according to the predefined inclusion and exclusion criteria, initially applied to titles and abstracts. Articles meeting the criteria will undergo a full-text review, applying the same criteria. Those eligible for inclusion will proceed to data extraction. Any disagreements encountered during this process will be resolved by consensus among the authors.

Two investigators will independently carry out the data extraction process, carefully reviewing the selected articles and transferring relevant information into a database created using Microsoft Excel 365 (Microsoft Corporation, Redmond, WA, USA). To ensure the accuracy of the process, all investigators will independently oversee the entire procedure and validate the extracted data.

Quality assessment / Risk of bias analysis The risk of bias assessment will be conducted during the data extraction process by two investigators. The designated tool for this purpose will be the 'Cochrane Collaboration tool for assessing risk of bias in randomized controlled trials.' (RoB-2). Any discrepancies will be resolved through general consensus.

Strategy of data synthesis Univariate metaanalysis models will be conducted to assess the primary outcome variables obtained from the systematic review (SR). For surgical clinical outcomes, the arithmetic mean difference (MD) and corresponding standard deviations (SD) will be used. The Restricted Maximum Likelihood (REML) method and inverse variance will be employed to estimate the weight of each study. A fixed-effects model will be applied when heterogeneity is low (50%). Additionally, univariate meta-analysis models will be performed to assess primary outcome variables related to adverse events, using the logarithmic form of the odds ratios (OR) estimated for these events. In this case, the Mantel-Haenszel method will be used, applying a fixed-effects model when heterogeneity is low (50%). Heterogeneity will be evaluated using Cochran's Q test and Higgins' I^2 statistic. Independent univariate meta-regression models will be conducted to explore sources of significant heterogeneity (>50%) and examine potential effect modifiers at the end of the meta-analysis model, including study- and patient-level covariates. These covariates or moderators will be selected post hoc based on the findings of the systematic review, considering variables that may influence the results. A funnel plot analysis and Egger's test will be conducted to assess the potential presence of publication bias in the studies included in the systematic review. The funnel plot will be used to visually examine the symmetry of studies based on sample size and estimated effect, helping to identify any potential biases related to study size. Subsequently, Egger's regression analysis will be employed to statistically evaluate the asymmetry of the funnel plot. In the case of detecting significant bias, additional analytical methods, such as sensitivity analysis, will be considered. Trial Sequential Analysis (TSA) will be conducted using the Trial Sequential Analysis Viewer software, version 0.95.10 (Beta; Copenhagen Trial Unit, Denmark). A two-sided alpha level of 5% and a statistical power of 80% will be applied. For binary outcomes, the incidence rates will be used; for continuous outcomes, the mean values, standard deviations, and empirically estimated variance will be included. In both cases, the O'Brien-Fleming alpha-spending function will be applied to adjust for cumulative testing and control the risks of type I and type II errors.

A p-value of ≤ 0.05 will be considered statistically significant. All analyses will be performed in RStudio 2024.12.0+467 (RStudio Team, Boston, MA, USA), using the 'Metafor' (v4.8-0) and 'Meta' (v8.0-2) packages.

Subgroup analysis A subgroup analysis will not be considered for this meta-analysis.

Sensitivity analysis A leave-one-out analysis will be conducted as part of the sensitivity analysis to assess the stability and robustness of the meta-analysis results in case significant biases are detected during the funnel plot analysis and Egger's test. This method will involve the sequential exclusion of each individual study to observe its impact on the overall estimated effect. If the removal of any study leads to a significant change in the results, it will be considered that such a study may have an excessive influence on the conclusions, allowing for the evaluation of the reliability of the meta-analysis findings.

Language restriction English language.

Country(ies) involved Mexico.

Keywords Retinal Diseases, Diabetic Retinopathy, Diabetic Angiopathies, Monoclonal Antibody, Vitrectomy.

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