INTRODUCTION

Review question / Objective: Our study aims to synthesise results from randomised controlled trials to assess the effectiveness and safety of PRP combined with intravitreous ranibizumab for T2PDR.

Rationale: Panretinal photocoagulation (PRP) can effectively improve the patient’s condition and intravitreous ranibizumab...
can effectively inhibit the retinal neovascularization. They were validated in large prospective, multicenter, randomized clinical trials, including the Diabetic Retinopathy Study, the Early Treatment Diabetic Retinopathy Study, the Diabetic Retinopathy Vitrectomy Study, and the Krypton-Argon Regression of Neovascularization Study. The mechanism of laser photocoagulation in the treatment of DR is as follows: the photocoagulation effect directly destroys the photoreceptor complex with high metabolism, replaces the collagen scar tissue with low oxygen consumption, thins the retina and reduces the oxygen consumption of the outer retina. High levels of VEGF aggravate the progression of the non-perfusion zone in both retinal vein occlusion and DR patients, suggesting that high levels of VEGF may lead to retinal vascular occlusion regardless of the disease course. So, intravitreal injection of anti-VEGF agents have become an interesting therapeutic method for T2PDR.

Condition being studied: Diabetic retinopathy (DR) is the most common complication of diabetes mellitus, which will seriously affect the quality of life of patients and bring great burden to patients’ families and society. DR is one of the most important diseases of blindness in people aged 20 to 60 years worldwide. Nearly 15% of diabetic patients with a disease duration of more than 5 years were combined with DR. The prevalence of vision threatening diabetic retinopathy in the United States is 4.4 percent. Worldwide, the prevalence is estimated at 10.2%. At present, the treatment methods for type 2 proliferative diabetic retinopathy (T2PDR), at home and abroad mainly include retinal laser photocoagulation and intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors.

METHODS

Search strategy: Electronic searches Two investigators (TL, WZ) will perform structured and systematic literature searches without interfering with each other in the following electronic bibliographic databases the China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Database, China Doctoral Dissertations Full-Text Database, China Master’s Theses Full-Text Database, Cochrane Central Register of Controlled Trials, PubMed, and Embase. The following medical subject headings terms were used for the search. “Total retinal photocoagulation”, “intravitreal ranibizumab”, “clinical RCT” and “type 2 proliferative diabetic retinopathy” and restricted the results to clinical trials. The search period of our study will be from the establishment of the database to March 15, 2022. Table 1 lists the search strategies that will be run in PubMed, with adjustments made to other databases as necessary. 2.2.2. Searching other resources In addition, relevant literature such as research papers, conference papers, ongoing experiments, and internal reports, among others and a first draft of a search strategy using PubMed as an example will also be retrieved.

Participant or population: Patients’ age will be between 18 and 75 years. Patients with type 2 proliferative diabetic retinopathy diagnostic criteria refer to stage V (except vitreous blood accumulation) in the international clinical classification of diabetic retinopathy. There are no restrictions on the duration of treatment or follow-up. Participants with unstable vital signs or inability to cooperate with treatment should be excluded, such as: (1) Combined with serious heart, liver, kidney and other important organs functional dysfunction; (2) Combined with other eye diseases (severe cataract, glaucoma, retinal vein occlusion, etc.); (3) taking coagulant and immunization within 1 month before treatment inhibitors, hormones and other drugs; (4) voluntary withdrawal for various reasons out of the experiment.

Intervention: Experimental group treated with total retinal photocoagulation combined with ranibizumab.

Comparator: The intervention in the control group will consist of: 1. Total retinal laser
photocoagulation only. 2. Treatment with ranibizumab medication only. 3. No intervention. The specific form options are as follows.

Study designs to be included: Only randomised controlled trials (RCTs) that were published or registered before 15 March 2022 will be included. Quasi-RCTs, review articles, case reports and other studies that do not meet the requirements will be excluded.

Eligibility criteria: Methods will vary by data type. For dichotomous variables, total effective rate and adverse events, we will analyse the rate ratio; for continuous variables, we will analyse mean differences. The 95% confidence interval will be presented for both dichotomous and continuous outcomes.

Information sources: Two investigators (TL, WZ) will perform structured and systematic literature searches without interfering with each other in the following electronic bibliographic databases the China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Database, China Doctoral Dissertations Full-Text Database, China Master's Theses Full-Text Database, Cochrane Central Register of Controlled Trials, PubMed, and Embase. Searching other resources - In addition, relevant literature such as research papers, conference papers, ongoing experiments, and internal reports, among others and a first draft of a search strategy using PubMed as an example will also be retrieved.

Main outcome(s): Primary outcomes. a.Best corrected visual acuity. b.Retinal vascular improvement, and macular central sulcus thickness reduction value. c.Retinal vascular improvement should include the presence of hemorrhagic areas, exudates, capillary non-perfused areas and blood rheology indicators in the retinal vessels.


Data management: Two researchers (TL, WZ) will read all selected studies and independently extract the following information: general information (title, authors, year of publication, journal); study details (design, randomization method); characteristics of participants (age, gender, sample size, duration of disease, inclusion/exclusion criteria); interventions (duration of single treatment, duration of treatment, combination treatment, follow-up time points); outcomes (primary and secondary outcomes). If the investigators cannot agree, a third investigator (QZ) will make the final decision. If insufficient or unclear data are reported, the original study authors will be contacted for more information.

Quality assessment / Risk of bias analysis: Assessment of risk of bias. Two independent reviewers (CL and XTL) will independently apply the bias tool from the Cochrane Handbook for Systematic Reviews of Interventions to evaluate the risk of bias in each selected study. The tool assesses the risk of bias in seven main areas: generation of randomised sequences, allocation concealment, blinding of patients, investigators and outcome assessors, incomplete outcome data, and selective reporting. Risk of bias in these areas will be assessed as low or high according to whether the criteria are met, and lack of information will be recorded as unclear, as recommended by the Cochrane Handbook. Disagreements will be resolved through discussion with third authors (ZXL) until consensus is reached.

Strategy of data synthesis: The meta-analysis of data from included outcomes will be performed using the RevMan V.5.4.1, and we will choose a randomized or fixed effect model for data statistics according to the results of the heterogeneity test. The enumeration data were expressed as relative risk (RR), and the weight mean difference (WMD) was used as the measurement data; each effect amount was expressed in 95% confidence interval (CI). The specific methods were as follows: If the heterogeneity was low (I² < 50%, the
fixed-effects model was used for data synthesis. If there is high heterogeneity ($I^2 > 50\%$), the random-effects model will be used for data synthesis after excluding possible heterogeneity sources. The investigation methods included subgroup and sensitivity analyses. If a meta-analysis cannot be performed, we will conduct a descriptive analysis.

**Subgroup analysis:** To address some potential issues, we will perform a subgroup analysis. First, we will compare the results of the clinical efficacy and acceptability of panretinal photocoagulation combined with ranibizumab in patients with T2PDR with PRP alone. Second, we will compare the results of PRP alone and in combination with other active treatments.

**Sensitivity analysis:** Sensitivity analysis. A sensitivity analysis will be performed to test the robustness of the review results and to detect sources of heterogeneity. This can be achieved by excluding trials with a high risk of bias or by eliminating each study individually. And, the impact of methodological quality, sample size, and missing data will be assessed. Then, after excluding studies with low methodological quality, the analysis will be repeated and the results will be compared to the previous meta-analysis.

**Language:** Language will not be restricted.

**Country(ies) involved:** China.

**Keywords:** panretinal photocoagulation, intravitreous ranibizumab, proliferative diabetic retinopathy, protocol, systematic review.

**Dissemination plans:** Ethics and dissemination: The protocol of the systematic review does not require ethical approval because it does not involve humans. The review will be published in a peer-reviewed journal.

**Contributions of each author:**

Author 1 - Ting Li conceived the study and provided general guidance to the drafting of the protocol.
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