Trials

STUDY PROTOCOL

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The effectiveness of vitrectomy co-adjuvant intravitreal dexamethasone implant on visual outcome in patients with proliferative diabetic retinopathy: study protocol for a prospective randomized controlled trial

Jipeng Li[1], Zhaoyang Wang[1], Aman Chandra[2,3], Jun Xu[1], Lin Liu[1] and Meng Zhao[1*]

Abstract

Background Proliferative diabetic retinopathy (PDR) often leads to tractional retinal detachment and vitreous hemorrhage, requiring vitrectomy. Poor visual outcomes are commonly caused by macular edema and proliferative vitreous retinopathy after vitrectomy. Intravitreal dexamethasone implant has shown promise in improving visual function after vitrectomy for diabetic macular edema, but its role in vitrectomy for PDR treatment remains unexplored. This study aims to assess the effectiveness of vitrectomy combined with an intravitreal dexamethasone implant for PDR patients.

Methods We will design a single-mask, randomized controlled trial with 100 participants diagnosed with PDR requiring vitrectomy. Participants will be randomly assigned to either the Ozurdex (0.7 mg dexamethasone intravitreal implant) group or the control group. The dexamethasone implant group will undergo vitrectomy combined with 0.7 mg dexamethasone intravitreal implant, while the control group will undergo vitrectomy alone. A single surgeon will perform all the vitrectomy surgeries, and the choice of intravitreal dexamethasone implant treatment will be disclosed before the closure of scleral wounds. Primary and secondary outcomes will be assessed at baseline and at 4, 8, 12, and 24 weeks post-vitrectomy.

Statistical analysis Statistical analysis will be conducted using R software. A p value 0.05 will be considered statistically significant. The analysis methods will include the following: visual acuity and OCT measurements will be analyzed using repeated measures analysis of variance (ANOVA) with two-tailed tests; rates of visual improvement, visual decline, postoperative vitreous hemorrhage, elevated intraocular pressure, and postoperative retinal detachment will be analyzed using chi-square tests with two-tailed tests. Logistic regression analysis will be used to analyze risk factors for poor visual prognosis, neovascular glaucoma development, and postoperative vitreous hemorrhage occurrence.

Discussion This protocol aims to enhance our understanding of the effects of combining an intravitreal Ozurdex 0.7 mg dexamethasone implant with vitrectomy on visual outcomes and macular morphology changes in treating late complications of PDR.

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Trial registration The trial was registered at the Chinese Clinical Trial Registry on May 11, 2022, with registration number ChiCTR2200059760.

Keywords Intravitreal dexamethasone implant, Vitrectomy, Proliferative diabetic retinopathy

Administrative information

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Introduction

Background and rationale {6a}

Proliferative diabetic retinopathy (PDR) is one of the major diseases threatening the vision of the working population [1]. In China, the prevalence of diabetes is high, and the incidence is rapidly increasing [2]. As PDR progresses to the stage of tractional retinal detachment or recurrent vitreous hemorrhage (VH), vitrectomy is often required to salvage the remaining vision [3–5]. However, a long-term follow-up study involving 217 PDR patients who underwent vitrectomy showed that the rates of low vision at 1 year, 5 years, and 10 years after surgery were 24%, 31%, and 39%, respectively. Most complications occurred within the first year after surgery, with the top three being elevated intraocular pressure (37%), macular edema (29%), and retinal detachment (12%) [6]. Additionally, there is often a certain degree of intraocular inflammatory response after vitrectomy surgery, which can lead to macular edema, vitreous cavity proliferative changes, affecting postoperative visual recovery, and possibly necessitating further surgery [7]. Diabetic patients often have complex systemic abnormalities, which limit systemic steroid use as a routine postoperative anti-inflammatory treatment.

Intraocular dexamethasone for diabetic macular edema (DME)

The intraocular dexamethasone sustained-release system, administered via a minimally invasive injection, has emerged as a delivery route for ocular therapeutics and has found widespread application in diabetic macular edema (DME) [8, 9]. It has been considered both effective and safe [10, 11].

Effectiveness of intravitreal dexamethasone injection for pars plana vitrectomy (PPV) in PDR

Recent studies have demonstrated the effectiveness of intravitreal dexamethasone (IVD) implants when used as an adjunct to PPV in patients with PDR: Altun et al. found that coadministration of IVD implant and silicone oil endotamponade during PPV for PDR with tractional diabetic macular edema (DME) (52 cases) resulted in significantly better visual acuity improvement and lower rates of DME development and intravitreal ranibizumab injection requirement compared to the control group [12]. Earlier small-scale clinical trials (23 patients followed for 6 months) have shown that combining vitrectomy in diabetic patients with intravitreal dexamethasone sustained-release system injection and silicone oil tamponade helps alleviate tractional macular edema and reduces the need for postoperative intravitreal injections of other anti-inflammatory agents (such as anti-vascular endothelial growth factor agents), and this combined treatment approach has been proven to be safe during follow-up [13]. Limon and Sezgin Akçay reported that using IVD with silicone tamponade in severe diabetic tractional retinal detachments (43 cases) significantly reduced rates of retinal re-detachment, PVR, anterior chamber fibrin exudation, and posterior iris synechia compared to controls without the dexamethasone implant [14]. Iglicki et al. in the TRADITION study observed significantly lower retinal re-detachment rates and less severe PVR at 6, 12,

and 24 months postoperatively in patients receiving the IVD implant during PPV compared to those without the implant [15]. Chalam et al. demonstrated that intravitreal dexamethasone significantly alleviates postoperative inflammation after vitreous surgery in patients with PDR, improving outcomes and reducing complications related to inflammation [16]. A prospective study involving patients with refractory DME following vitrectomy (55 patients over 26 weeks) demonstrated that intravitreal injection of the dexamethasone sustained-release system after vitrectomy is a safe and effective treatment modality [17].

Gap in research for PDR

However, the severity of PDR was not addressed in these aforementioned studies, and there is a scarcity of case reports on PDR cases involving tractional retinal detachment in the macular area. Limited reports are available for severe PDR cases that did not undergo preoperative retinal laser therapy [12, 13]. Therefore, there exists a research gap in the observation of patients with severe, untreated PDR. These patients often require complex surgical interventions due to extensive peripheral retinal detachments, which include combined cataract surgery, intraoperative pan-retinal photocoagulation, and postoperative gas tamponade, thereby increasing the likelihood of postoperative inflammatory reactions.

Objectives {7}

In China, many diabetic patients experience untreated progressive PDR lesions. These patients often present with recurrent vitreous hemorrhage and tractional retinal detachment involving the macula at the initial consultation, with a lack of adequate previous photocoagulation or intravitreal anti-VEGF treatments. Such patients often require extensive intraoperative laser therapy and intraocular tamponade, leading to potentially heightened postoperative inflammatory responses.

The study aims to address limitations in prior research by collecting a diverse and complex group of PDR patients. This will allow for a thorough evaluation of the efficacy and safety of the combination treatment with intravitreal dexamethasone and vitrectomy in managing progressive DR. By focusing on a wider variety of untreated PDR cases, we aim to examine both visual and inflammatory outcomes post-surgery.

Primary hypothesis

The hypothesis is that combining vitrectomy with intravitreal dexamethasone will result in more effective reduction of postoperative macular edema and improved visual function compared to vitrectomy alone.

Secondary hypotheses

Combining these treatments will minimize postoperative inflammatory responses compared to vitrectomy alone.

It will also result in improved resolution of diabetic macular edema (DME).

Postoperative complications such as vitreous hemorrhage and intraocular pressure fluctuations will be reduced.

Justification for outcome measures

Postoperative macular edema: Based on previous research findings, the incidence of postoperative macular edema in PDR is 29%, with 18% occurring within 1 year post-surgery [6]. In PDR patients who had pre-existing macular edema before surgery, the rate of resolution of macular edema after vitrectomy is only 22.9–29% [14]. Measuring postoperative macular edema will help assess the primary hypothesis that the combination treatment improves its resolution and reduces its incidence.

Visual function improvement: Corrected visual acuity (LogMAR visual acuity chart) will be measured to evaluate the primary outcome of visual function improvement, as it is a universally recognized efficacy indicator for surgical treatment of PDR.

Postoperative inflammatory reactions: The degree of intraocular inflammation post-surgery will be assessed to test the hypothesis that the combination treatment reduces inflammatory responses.

Postoperative complications: The incidence of postoperative vitreous hemorrhage, retinal reattachment rate, and intraocular pressure fluctuations will be measured to evaluate the safety and efficacy of the combination treatment. These are common postoperative complications and recognized efficacy indicators for surgical treatment.

Resolution of DME: Central macular thickness on OCT will be measured to observe changes in macular morphology, providing insight into the secondary hypothesis regarding DME resolution.

Study design

Therefore, this study aims to conduct a prospective randomized controlled trial on patients with untreated PDR requiring vitrectomy. The study will compare vitrectomy combined with intravitreal dexamethasone sustained-release implant system injection to vitrectomy alone, focusing on postoperative inflammatory reactions, visual improvement, resolution of DME, and common

postoperative complications such as postoperative VH and intraocular pressure fluctuations.

By collecting a diverse group of complex PDR patients, this study aims to provide a comprehensive evaluation of the effectiveness and safety of combining intravitreal dexamethasone with vitrectomy for progressive diabetic retinopathy (DR).

Trial design {8}

A single-masked randomized controlled trial will be conducted to compare the effects of vitrectomy combined with an intravitreal dexamethasone implant versus vitrectomy alone (Fig. 1). The study will be conducted over a period of 24 weeks (6 months), which includes a follow-up period. Primary outcomes will be measured at baseline, 4, 8, and 12 weeks, while secondary outcomes will be measured at baseline, 4, 8, 12, and 24 weeks. The allocation ratio is set at 1:1. The framework is exploratory [15].

Methods: participants, interventions, and outcomes [15, 16]

Study setting {9}

Beijing Tongren Eye Center, a tertiary academic hospital, will serve as the primary site for the study. The data will be collected at the same center.

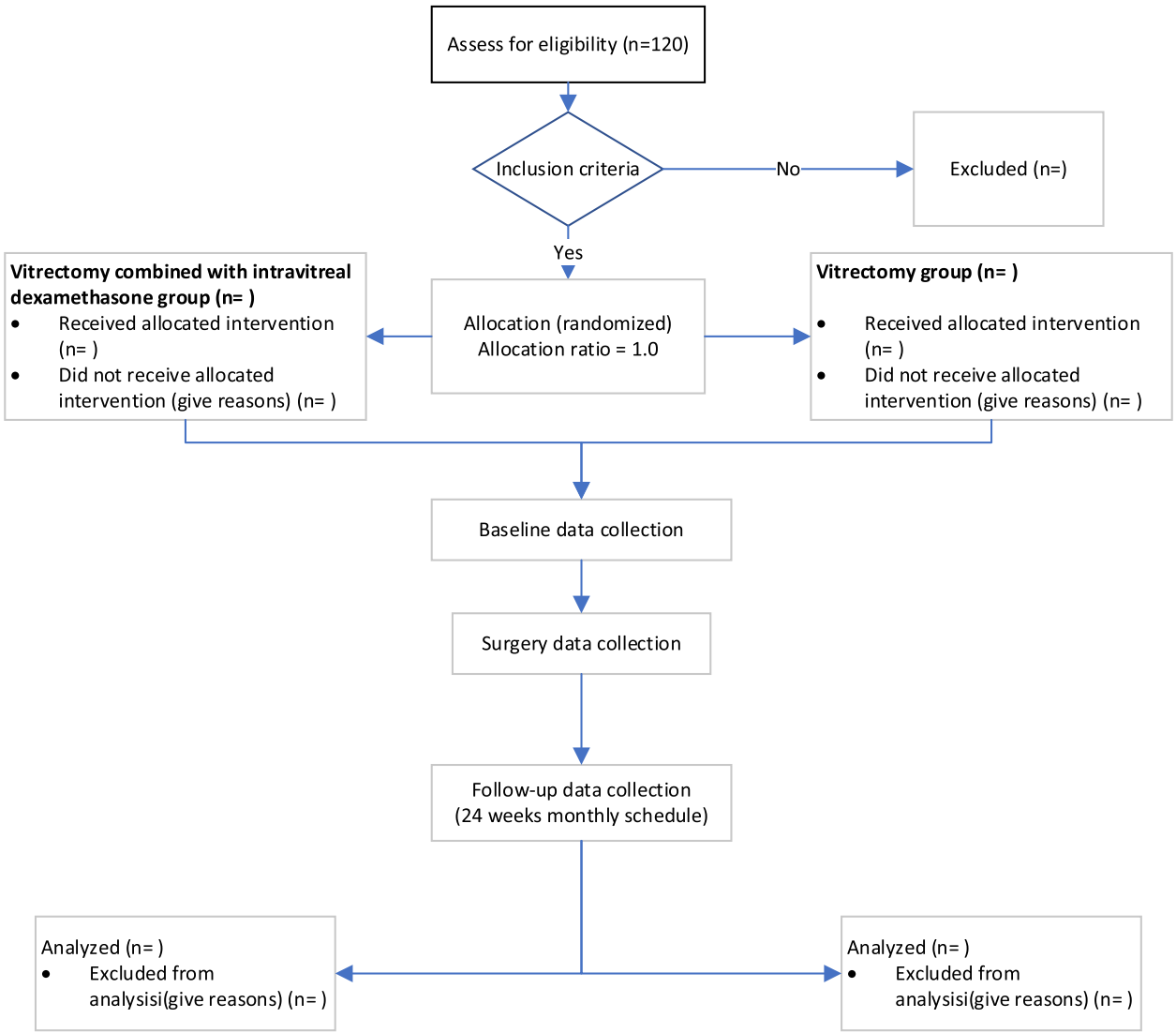

Fig. 1 A single-masked randomized controlled trial

Eligibility criteria {10}

Inclusion criteria

1. Patients with PDR will be included in the study if they meet one of the following three criteria: (1) presence of tractional retinal detachment involving the macula or an area adjacent to the macula, as confirmed by clinical examination; (2) presence of recurrent or non-absorbing vitreous hemorrhages; (3) simultaneous presence of vitreous hemorrhage and tractional retinal detachment confirmed by B-scan ultrasound examination when the fundus was obscured by vitreous hemorrhage.
2. Age between 18 and 70 years.
3. Willingness to participate in the study and comply with scheduled follow-up visits.

Exclusion criteria

Participants will be excluded from the study if any of the following conditions are reported:

1. Presence of severe uncontrolled systemic abnormalities that contraindicated to vitrectomy surgery
2. Recent (< 3 months) administration of other intravitreal dexamethasone implant
3. History of glaucoma
4. History of conditions that may cause macular edema, such as uveitis or retinal vein occlusion
5. History of previous vitrectomy
6. Intraoperative identification of vitreous hemorrhage not caused by PDR

Who will take informed consent? {26a}

The primary investigator will obtain informed consent from the potential trial participants.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

No secondary participant information or data will be collected, nor any biological specimens will be collected.

Interventions

Explanation for the choice of comparators {6b}

The two comparators in this study are the vitrectomy combined with intravitreal dexamethasone implant group and the vitrectomy alone (control) group. These comparators were selected to evaluate the impact of vitrectomy combined with an intravitreal dexamethasone implant on the visual outcomes and macular morphology of individuals with PDR during the 24-week post-vitrectomy period. By comparing these outcomes with those of individuals who underwent vitrectomy alone, the study aims to assess the effectiveness and safety of the intervention. The inclusion of a control group receiving vitrectomy alone allows for a comprehensive and clinically relevant evaluation of the intervention's effects in comparison to established treatment options. This approach ensures that the study findings can be extrapolated to real-world clinical practice, facilitating evidence-based decision-making in the management of PDR.

Intervention description {11a}

Vitrectomy

The patients underwent retrobulbar or general anesthesia. All patients underwent 23/25 gauge 3-port pars plana vitrectomy (PPV) using the Constellation Vision System (Alcon, Fort Worth, TX, USA). Patients with active fibrovascular epiretinal proliferative membranes (FVMs) or severe vitreous hemorrhage (VH) obscuring the fundus received intravitreal ranibizumab (IVR) within 7 days prior to vitrectomy, and the pre-vitrectomy IVR administration was documented. Following core vitrectomy, the presence of FVM, macular-involving tractional retinal detachment (TRD), and photocoagulation scars were documented. Triamcinolone acetonide-assisted vitrectomy was performed, releasing anterior–posterior vitreoretinal traction and inducing posterior vitreous detachment. Dissection, segmentation, delamination of FVM, endodiathermy, drainage of subretinal fluid, retinectomy, and intraocular tamponade were performed as needed for each patient. Peripheral vitrectomy with scleral indentation and endolaser photocoagulation were performed for all patients. Intraoperative bleeding was managed using techniques such as intraocular pressure elevation, perfluorocarbon liquids, and endodiathermy.

Intravitreal dexamethasone implant

At the end of vitrectomy and before the closure of the scleral incision, a dexamethasone implant (Ozurdex®; Allergan, Inc., Irvine, CA, USA), which contains 0.7 mg of dexamethasone in a sustained-release formulation, was injected into the vitreous from the incision.

Vitrectomy combined with intravitreal dexamethasone implant group

Patients in this group will receive vitrectomy and an intravitreal dexamethasone implant at the end of vitrectomy.

Vitrectomy group

Patients in this group will receive vitrectomy only.

Criteria for discontinuing or modifying allocated interventions {11b}

Discontinuation criteria

Observation endpoints for study discontinuation were defined as follows: (1) patient completion of the 6-month follow-up period; (2) patient requiring a second surgery for non-attached retina or non-absorption of vitreous hemorrhage; (3) patient undergoing glaucoma surgery due to poor control of intraocular pressure with medication (including secondary to intraocular tamponade, uncontrolled neovascular glaucoma, or medication-induced); (4) occurrence of uncontrolled intraocular inflammation; (5) surgical removal of dislodged implant from the anterior chamber; (6) deterioration of the patient's overall systemic condition preventing further follow-up; (7) loss of visual acuity during the follow-up period or patient withdrawal from the treatment.

Strategies to improve adherence to interventions {11c}

All participants will receive preoperative education on PDR from the surgeon, emphasizing the significance of regular follow-up visits. During each follow-up appointment, scheduled plans for the next 6 months will be discussed individually with the participants, taking into consideration their availability and schedules. In the event that participants fail to adhere to the monthly follow-up schedule, the principal investigator (PI) will proactively contact the participant to ascertain the reasons for delayed presentation and investigate any underlying factors and rearrange the new schedule for follow-up if the participant could continue the previous follow-up plan.

Relevant concomitant care permitted or prohibited during the trial {11d}

No concomitant care and intervention requirements are either permitted or prohibited during the trial. The participants will be asked to maintain their medication dosage and any mandatory medical care or aid that they are receiving during the intervention period.

Provisions for post-trial care {30}

N/a.

Outcomes {12}

All outcome measures will be conducted by the researchers, binding to group allocation, at baseline and at 4-, 8-, 12-, and 24-week follow-up after vitrectomy.

Demographics, including age; gender; preoperative characteristics, including DM duration and DM medication, and the history of diabetes-related complications, including stroke, coronary artery disease (CAD), congenital heart failure, diabetic foot and chronic kidney disease, and hypertension; anticoagulation or antiplatelet medications; and ocular characteristics, including the history of previous photocoagulation, cataract phacoemulsification extraction, IV anti-VEGF agents, and visual symptom duration will be collected.

All the patients will go through a comprehensive ocular examination after enrollment, including corrected visual acuity (VA) tested by a Snellen decimal VA chart, intraocular pressure test by non-contact tonometer, silt lamp examination to evaluate lens status and the presence of iris neovascularization and neovascular glaucoma, binocular indirect ophthalmoscopy examination to evaluate severity of VH and FVP, B-scan ultrasound examination to identify retinal detachment, and OCT scan to evaluate macular morphology if possible.

Primary outcome measures

The primary outcome measures in this research protocol include corrected visual acuity at 12 weeks post-treatment. Baseline visual acuity and corrected visual acuity at 4, 8, and 12 weeks post-treatment will be measured using the LogMAR visual acuity chart.

The assessment of corrected visual acuity will not involve the collection of biological samples. Corrected visual acuity serves as a universally recognized efficacy indicator for surgical treatment of PDR eyes.

Secondary outcome measures

The secondary outcome measures in this research protocol encompass the following parameters:

1. Retinal reattachment rate at 24 weeks post-vitrectomy evaluated by fundus examination using indirect binocular ophthalmoscopy.
2. Central macular thickness on OCT at 12- and 24-weeks post-vitrectomy.
3. Incidence of intraocular pressure elevation recorded at 12- and 24-weeks post-vitrectomy.
4. Incidence of occurrence of postoperative vitreous hemorrhage during the 24-week follow-up after vitrectomy evaluated by fundus examination using indirect binocular ophthalmoscopy.
5. Occurrence of subsequent cataract surgery in the following 24 weeks after vitrectomy.
6. Incidence of choroidal detachment within 4 weeks post-vitrectomy.

Among these measures, the retinal reattachment rate, incidence of postoperative vitreous hemorrhage, and occurrence of choroidal detachment are recognized efficacy indicators for surgical treatment. The

rates of intraocular pressure elevation and subsequent cataract surgery serve as safety indicators for intraocular implantation. Central macular thickness on OCT is a widely accepted metric for evaluating macular morphology.

The inclusion of these secondary outcome measures allows for a comprehensive evaluation of treatment efficacy, safety, and specific macular morphology changes associated with the intervention.

Participant timeline {13}

Sample size {14}

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3	t_4	t5.	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
Vitrectomy combined dexamethasone implant		X						
Vitrectomy		X						
ASSESSMENTS:								
[baseline variables:demographic details, past history on DM and DR, corrected VA, severity of PDR]	X	X						
[corrected VA and CRF]			X	X	X			X
[retinal attachment, VH, IOP, further ocular surgery]			X	X	X	X	X	X

The estimated number of participants needed to achieve the study's objectives is 39 per group. This calculation is based on achieving a 93% statistical power to detect a difference between the means of the independent variables for testing the hypotheses, with an alpha level of 5% and a minimal clinically important difference (MCID) of 1.13. The MCID was determined based on values obtained from past published studies [6, 17, 18], which evaluated similar interventions in PDR patients.

Assumptions and parameters

Expected effect size: The expected effect size was derived from previous studies that demonstrated significant differences in outcomes such as visual acuity and macular thickness following similar interventions.

Standard deviation: The standard deviation was estimated based on historical data from these studies, accounting for variability in the primary outcome measures.

Alpha level: 5%.

Power: 93%.

MCID: 1.13.

Considering a 10–15% dropout rate during the 24-week follow-up, we estimated the need for 50 participants per group. The dropout rate assumption is based on similar studies involving interventions for PDR, where dropout rates ranged from 10 to 15% [reference similar studies if available]. This adjustment ensures that the study remains adequately powered to detect clinically meaningful differences despite potential participant attrition.

Recruitment {15}

Participants with PDR requiring vitrectomy will be recruited from the outpatients' clinics at Tongren Eye Center between October 2022 and October 2024 (the duration of patient recruitment is 2 years from the date of approval). The recruitment process will involve two sources, as outlined below:

1. Three retinal specialists, who collectively encounter over 60 PDR patients on a weekly basis, will oversee the recruitment of participants. These specialists will identify and approach eligible individuals for potential inclusion in the study.
2. Diabetic patients present at physicians at Tongren Hospital will be referred to the participated ophthalmologists for further evaluation of their DR condition. The referral process will specifically target patients suspected or known to have PDR, who may require vitrectomy. These patients will then be considered for potential enrolment in the study.

Assignment of interventions: allocation

Sequence generation {16a}

The allocation of participants in this study will be performed through a process of computer-generated random numbers. The enrolled participants will be randomly assigned to one of two groups: the vitrectomy combined with intravitreal dexamethasone implant group and the vitrectomy-only group. The ratio of participants assigned to each group will be 1:1, without any additional stratification.

To ensure the integrity of the randomization process, the randomized numbers will be generated by a computer and provided in a separate document. This document will remain inaccessible to individuals involved in patient enrollment or the performance of vitrectomy. By maintaining the confidentiality of the randomized number assignment, we aim to minimize any potential biases or influences on participant allocation.

Concealment mechanism {16b}

The randomization design will use permuted block sizes of 4 and 6 with the participant assignments placed in opaque, sealed, and serially numbered envelopes and individualized for each participant.

Implementation {16c}

The randomization schedule will be generated by the data analyst (ZM), who will deliver this document in a sealed envelope to the surgeon (LJP) responsible for assigning the participants to the two groups.

Assignment of interventions: masking

Who will be masked to group assignment {17a}

In this randomized, single-mask controlled trial, it is crucial to maintain masking for both the participants and the data analysts after assignment to the intervention groups.

Participant masking

To ensure participant masking, measures will be taken to prevent participants from discerning their assigned treatment group. These include:

Using identical packaging and labeling for both the investigational drug and the comparator/placebo to avoid any visual distinction.

Ensuring real-time insurance settlement for the patients, so there is no direct financial transaction or reimbursement process that might reveal the treatment group.

Adding a provision in the informed consent during ethical review, stating that if secondary reimbursement through commercial insurance is necessary, the medical records involving treatment group details will only be released to the patient after they reach the observation endpoints for study discontinuation.

Avoiding explicit communication about the treatment, ensuring that patients are not informed of their assigned group during the study process.

Data analyst masking

The data analyst responsible for data analysis and outcome assessments will also be kept mask to the treatment allocation. This will be achieved by:

Withholding information regarding the assigned interventions in the data provided for analysis.

Masking or removing any identifying details that may inadvertently reveal the treatment group from the dataset.

Minimizing bias in outcome assessment

To minimize bias in outcome assessment, the following steps will be implemented:

Blinded outcome assessors: Outcome assessments will be conducted by trained, independent assessors who are masked to the treatment allocation. These assessors will not be involved in the surgical procedures or follow-up evaluations.

Standardized assessment protocols: All outcome assessments will follow standardized protocols to ensure consistency and objectivity. This includes using objective measurement tools and predefined criteria for evaluating outcomes.

Centralized data review: Data analysis will be performed centrally by a team that is mask to treatment allocation, further reducing the potential for bias.

Unmasking procedure if needed {17b}

Unmasking of participants to their assigned interventions will be conducted under specific circumstances, following predefined criteria. The unmasking procedure will be implemented as outlined below:

1. Health emergencies: If a participant's overall health condition significantly worsens and poses a threat to their life, unmasking will be initiated to ensure appropriate medical management and intervention.
2. Elevated intraocular pressure (IOP): In cases where the participant experiences elevated IOP exceeding 30 mmHg with suboptimal response to medication, unmasking will be considered.
3. Intraocular inflammation: Unmasking may also occur if the participant develops significant intraocular inflammation, indicating the need for specialized treatment and care.

The process of unmasking will be carefully conducted by authorized individuals who are not involved in the primary assessment or outcome evaluation. These individuals will have access to the allocation information, which will remain confidential throughout the study duration. If emergency unmasking occurs in more than 20% of cases before the completion of the trial, it will be deemed a failure of the single-mask trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

To ensure data quality, we employ various processes, including duplicate measurements and rigorous training of assessors.

The data will be entered through an on-line web browser input form designed at JianDao Cloud platform. The Epidata EDC system will be used for data collection. Patient data will be documented by dedicated trial personnel and managed in the eCRF. All staff involved in the data collection process are to be qualified to access the research database.

Our study utilizes specialized ophthalmic examination and surgical equipment, including standard devices for intraocular pressure measurement, visual acuity assessment, vitrectomy, and OCT scans. All measurements strictly adhere to clinical trial protocols, ensuring data precision and accuracy for proliferative diabetic retinopathy vitrectomy procedures.

The data entry forms are stored within the JianDao Cloud platform, where duly authorized researchers gain access through mobile phone number verification.

Plans to promote participant retention and complete follow-up {18b}

To ensure participant retention and data completeness, we will emphasize the importance of scheduled follow-up appointments through education. During clinical encounters, we will discuss and schedule follow-up visits with participants and their families. Additionally, a designated staff member will perform telephone follow-ups for participants exceeding a 2-week follow-up gap. To address potential non-compliance or attrition, we have outlined specific outcome data collection. This streamlined approach aims to maximize research integrity and data collection even in cases of participant non-compliance or attrition.

Criteria for discontinuing or modifying interventions

Participants may discontinue or modify their interventions based on the following criteria:

1. Completion of follow-up: Patients completing the 6-month follow-up period.
2. Secondary surgery: Patients undergoing secondary surgery due to retinal detachment with non-repositioning or non-absorption of vitreous hemorrhage.
3. Glaucoma surgery: Patients requiring glaucoma surgery due to inadequate control with ocular hypotensive medications (including cases secondary to fillers, uncontrolled neovascular glaucoma, or medication-induced).
4. Intraocular inflammation: Incidence of significant intraocular inflammation that necessitates intervention.
5. Surgical removal of implant: Surgical removal of an implant dislocated into the anterior chamber.

6. Deterioration of general health: Deterioration of the patient's general health that prevents further follow-up.
7. Visual loss or treatment discontinuation: Significant visual loss or patient discontinuation of treatment during the follow-up period.

Standardization of decisions

To ensure consistency in how these decisions are applied across all participants, the following procedures will be implemented:

Centralized review: All decisions to discontinue or modify interventions will be reviewed by a centralized clinical review board consisting of experienced ophthalmologists and trial investigators.

Standard operating procedures (SOPs): Detailed SOPs will be developed and followed to guide the clinical review board in making standardized decisions based on the specified criteria.

Documentation and communication: All decisions and the reasons for discontinuation or modification of interventions will be thoroughly documented and communicated to all relevant study personnel to maintain consistency.

Training: Study staff and investigators will be trained on the criteria and SOPs to ensure uniform application of these guidelines.

Follow-up data collection: Outcome data for participants who discontinue the study will include the specific reasons for discontinuation or modification, ensuring comprehensive data collection for analysis. Monthly reviews of clinical research issues are conducted, categorized by deviation severity. All protocol deviations are documented in a Protocol Deviation Report, detailing discovery time, event timelines, reasons, and corrective actions. Severe deviations affecting subject rights, safety, or data integrity are reported to regulatory authorities and ethics committees, outlined in the research plan. In masked studies, protocol deviations are managed separately for masked and unmasked teams, with specialized unmasked team review. Severe deviations may lead to data exclusion from specific analysis populations. Mild deviations, not classified as severe, will not trigger data exclusion unless they recur and become severe.

This approach ensures that decisions to discontinue or modify interventions are made consistently and transparently, thereby maintaining the integrity of the study and the validity of the results.

Data management {19}

Data collection entails a meticulous process characterized by the independent entry of data by two trained staff members. Subsequently, Epidata is utilized to assess data consistency. In cases of inconsistency, a third staff is involved for data verification and validation. This rigorous protocol ensures data integrity, aligning with the highest standards of research precision.

The principal investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Confidentiality {27}

We prioritize participant data confidentiality throughout the trial, in compliance with national data protection laws and WHO Good Clinical Practice guidelines. All patient data, including case report forms, is securely managed to maintain privacy during and after the trial.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/a

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

This study will use R for statistical analysis of data. A p value < 0.05 will be considered statistically significant.

Analysis plan

Primary and secondary outcomes Visual acuity and OCT measurements: These will be analyzed using repeated measures analysis of variance (ANOVA) with two-tailed tests to account for the repeated measurements at baseline, 4, 8, 12, and 24 weeks.

Rates of visual improvement, visual decline, postoperative vitreous hemorrhage, elevated intraocular pressure, and postoperative retinal detachment: These categorical outcomes will be analyzed using chi-square tests with two-tailed tests.

Descriptive statistics Normal continuous data: Described using mean and standard deviation.

Non-normally distributed continuous data: Described using median and quartiles.

Categorical variables: Described using proportions and rates.

Grouping variables For continuous data, t-tests or rank-sum tests will be used, depending on the normality of the data distribution.

For categorical variables, chi-square tests or Fisher's exact tests will be used.

Risk factor analysis Analysis of risk factors for poor visual prognosis, neovascular glaucoma development, and postoperative vitreous hemorrhage occurrence will be conducted using logistic regression analysis.

Interim analyses {21b}

Interim analysis will be conducted after 1 year of study initiation or when 50% of the medical records have been collected. The interim analysis will be carried out by PI and members who are in charge of statistic analysis, who will then decide whether to terminate the trial based on the results.

Formal stopping rules for the study are as follows:

> If any patient develops conditions listed in the discontinuation criteria, the study team will convene to review the case.
> The decision to formally stop the study for an individual patient will be made by the PI in consultation with the study's Data and Safety Monitoring Board.
> The Data and Safety Monitoring Board will evaluate the safety and efficacy data at interim analysis points and recommend stopping the trial if the risks to participants outweigh the potential benefits or if significant adverse events are observed.
> The trial will be formally terminated if a predetermined safety threshold is reached, as defined in the protocol, to ensure participant safety.

Methods for additional analyses (e.g., subgroup analyses) {20b}

There are no planned subgroup analyses.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Handling missing data

Missing data will be handled using multiple imputation methods to ensure the robustness of the analysis. The multiple imputation technique will be used to replace missing values with a set of plausible values based on the distribution of the observed data. Sensitivity analyses will be conducted to assess the impact of missing data on the study results.

Intention-to-treat analysis

All analyses will be conducted on an intention-to-treat (ITT) basis, meaning that all participants will be analyzed in the groups to which they were originally assigned, regardless of whether they completed the intervention according to the protocol. This approach preserves the benefits of randomization and provides a more conservative estimate of the treatment effect.

By including these detailed statistical methods, handling of missing data, and the intention-to-treat analysis, we ensure a comprehensive and rigorous approach to data analysis that aligns with best practices in clinical research.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

Access to the full protocol, participant-level dataset, and statistical code will be granted upon reasonable request. The datasets analyzed during the current study, as well as the statistical code, are available from the corresponding author on reasonable request.

Public and patient involvement

Although there was no direct involvement of patients or the public in the design of this protocol, we recognize the importance of patient-centered care and active participation throughout the research process. Future studies will aim to include patient and public involvement in the research design to ensure the research is aligned with patient needs and perspectives.

Oversight and monitoring

The Project Management Group oversees the day-to-day running of the trial and meets quarterly to review trial conduct and ensure compliance with the protocol. The Trial Steering Group meets biannually to discuss trial progress, safety, and emerging issues, while the independent Data Monitoring and Ethics Committee convenes annually to review safety and efficacy data. These committees provide organizational support and oversight throughout the trial.

Composition of the coordinating center and trial steering committee {5d}

Composition of the data monitoring committee, its role and reporting structure {21a}

No special data monitoring is needed for this single-center research.

Adverse event reporting and harms {22}

Any adverse medical events occurring from the patient's signing of the informed consent form to their last

follow-up, whether causally related to the experimental drug, are considered adverse events. These events are reported and managed following hospital protocols, and records include event timing, severity, duration, interventions, and outcomes.

Adverse events are defined as those resulting in death, life-threatening situations, hospitalization, extended hospital stays, or permanent/severe disability/loss of function. After an adverse event, it is reported to relevant departments, and management follows the guidance of department consultations, adhering to hospital protocols.

Frequency and plans for auditing trial conduct {23}

The trial will be audited by the Ethics Committee of Beijing Tongren Hospital on a yearly basis. In addition, the Project Management Group will meet quarterly to review trial conduct and ensure compliance with the protocol. The Trial Steering Group and the independent Data Monitoring and Ethics Committee will also review the conduct of the trial throughout its duration. The Trial Steering Group will meet biannually to discuss trial progress, safety, and any emerging issues. The Data Monitoring and Ethics Committee, given the low-risk nature of the intervention, will convene annually unless specific concerns arise that warrant more frequent meetings. All relevant auditing activities and findings will be documented and reviewed to maintain the highest standards of trial conduct.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Ethical considerations

1. Informed consent

Process: Informed consent will be obtained from all participants before their inclusion in the study. The consent process will involve providing participants with detailed information about the study's purpose, procedures, potential risks, benefits, and their rights as participants.

Documentation: Participants will be given an informed consent form to read and sign. This form will be approved by the Ethics Committee and will include all necessary information in an understandable format.

Discussion: Investigators will discuss the study with each participant, answer any questions, and ensure they fully understand the information before consenting. Participants will be informed that their participation is voluntary and that they can withdraw from the study at any time without any negative consequences.

2. Participant confidentiality

Data protection: All participant information will be kept confidential. Personal identifiers will be removed, and unique study codes will be used to label data.

Access control: Only authorized study personnel will have access to participant data. Data will be stored in secure, password-protected databases.

Compliance: The study will comply with relevant data protection regulations, including the General Data Protection Regulation (GDPR) if applicable, and local laws.

3. Protocol modifications

Approval by Ethics Committee: The principal investigator (PI) will seek approval from the Ethics Committee for any proposed changes to the protocol.

Communication with investigators: After receiving approval from the Ethics Committee, the PI will notify all relevant investigators of the approved amendments.

Documentation: A copy of the revised protocol will be added to the Investigator Site File.

Deviation documentation: Any deviations from the protocol will be fully documented using a breach report form.

4. Registry update: We will update the protocol in the Chinese Clinical Trial Registry (ChiCTR), where the study is registered (Registration number: ChiCTR2200059760).

Dissemination plans {31a}

We plan to communicate trial results to participants, healthcare professionals, and the public through multiple channels:

1. Publications

We will submit the trial results for publication in peer-reviewed scientific journals to reach the academic and medical communities.

2. Presentations

Results will be presented at national and international conferences to disseminate findings to a wider audience of healthcare professionals and researchers.

3. Results databases

The trial results will be reported in relevant clinical trial results databases to ensure transparency and accessibility.

4. Participant communication

Participants will be informed of the trial results through newsletters or summary reports, ensuring they are aware of the study outcomes.

5. Public outreach

Efforts will be made to communicate the results to the general public through press releases and media engagements to enhance public understanding and awareness of the findings.

By providing detailed information on ethical considerations and a comprehensive plan for the dissemination of results, we aim to ensure the ethical conduct of the study and the broad communication of its findings.

Discussion

This study is a prospective randomized controlled trial, and there is no similar research available on the efficacy of intravitreal dexamethasone combined with vitrectomy in the treatment of PDR. Prior studies have confirmed that the incidence of macular edema following pars plana vitrectomy in PDR patients is high, making it one of the primary factors affecting visual prognosis [4]. Therefore, this study aims to shed light on the role of intravitreal dexamethasone in alleviating macular edema and improving visual outcomes in PDR patients after vitrectomy.

A key issue in this research lies in the execution of masking. The dexamethasone drug used in the study is white in color. To minimize any potential influence on the surgeon's decisions during vitrectomy, we chose to unmask and administer the injection at the time of closing the incisions. During follow-up, the implant may be located either in the vitreous cavity or anterior to the retina and may be visible. Therefore, the informed consent documents for patients explicitly state that patients should not be concerned about the presence or absence of linear shadows post-surgery and should adhere to the scheduled follow-up visits. However, for the physicians responsible for postoperative examinations, indirect ophthalmoscopy fundus examination may reveal the presence of the implant in the vitreous cavity. Therefore, masking is not feasible for postoperative follow-up doctors, surgeons at the end of the surgery, and patients who perceive distinctive dark shadows in their vision. However, masking can be maintained for the surgeon preoperatively, patients preoperatively, individuals involved in data collection and analysis, and patients without clear distinctive dark shadows postoperatively. As a result, this study is a clinical research utilizing masking in a single-mask, randomized controlled trial manner and cannot achieve double-masking.

Due to the majority of patients being non-local, postoperative follow-up poses some challenges. We have employed strategies such as preoperative education on the importance of post-vitrectomy follow-up, prescheduled appointments, and the use of follow-up forms to remind both the follow-up doctors and patients to ensure timely completion of follow-up visits. During the follow-up process, a designated person is responsible for promptly identifying patients who have not attended follow-up visits for more than 2 weeks. We will communicate with these patients through phone calls to encourage them to return for follow-up, and for those unable to visit, PI is responsible for conducting telephone tracking as outlined in the pre-designed tracking protocol and rearranging the missed follow-up for the patients.

In the statistical analysis, vision and OCT thickness measurements are subjected to repeated-measures analysis of variance. To ensure that the results are minimally affected by measurement variations across different devices, we employ the same measurement personnel for corrected vision measurement and the same instrument for OCT retinal thickness measurement. To ensure an adequate sample size for the efficacy analysis of diabetic retinopathy macular edema, we estimated the sample size based on reported rates from prior literature and our pre-experimental results of postoperative macular edema incidence, adding a 10–15% of dropout rate of the participants during the 24-week follow-up.

Trial status

The version of the protocol is 20,220,909. The date of the approval of the protocol is September 29, 2022. The recruitment began on November 23, 2022; it will be completed on December 4, 2023.

Abbreviations

CRT	Central retinal thickness
DME	Diabetic macular edema
DR	Diabetic retinopathy
FVM	Fibrovascular vascular membranes
IVR	Intravitreal ranibizumab
PDR	Proliferative diabetic retinopathy
PI	Primary investigator
OCT	Optic coherence tomography
VH	Vitreous hemorrhage

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Authors' contributions {31b}
Jipeng Li is the primary investigator; he led the proposal and protocol development. Meng Zhao contributed to study design and to development of the proposal; she was the trial methodologist. Jun Xu is in charge of disclosing the mask and the follow-up of the patients. Lin Liu is in charge of scheduling the visiting of the patients, entering data and storing the record sheet and education about the follow-up. Aman Chandra is in charge of study design, supervision of the study data collection, and revising the manuscript. Zhaoyang Wang is in charge of the follow-up of the patients during Jun Xu's absence and participating data analysis and revision of manuscripts.

Funding {4}
This study does not have external funding. All costs associated with the study, including the intravitreal dexamethasone implants and other related expenses, will be paid by the patients themselves

Data availability {29}
In this study, only members of the research team will have access to the data.

Declarations

Ethics approval and consent to participate {24}
The study followed the tenets of the Declaration of Helsinki and the protocol and was approved by the Institutional Review Board of Beijing Tongren Hospital (TREC2022-KY063) on August 30, 2022. Patients were required to sign an informed consent form, and written informed consent was obtained from each participant.

Consent for publication {32}
Not applicable.

Competing interests {28}
The authors declare that they have no competing interests.

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