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A Randomized Prospective Study on the Timing of Ranibizumab Administration before Vitrectomy in Patients with Severe Diabetic Retinopathy: Assessing Complications, Visual Outcomes, and Retinal Traction Development

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Currently, proliferative diabetic retinopathy (PDR) and diabetic macular oedema (DMO) are recognised complications of diabetes mellitus (DM) and rank among the top five leading causes of blindness and visual impairment worldwide, including among working-age individuals. The only pathogenetically justified treatment for PDR complicated by cataract and DMO with vitreomacular traction is surgery. This approach aims to restore optical media transparency, remove fibroglial tissue (FGT), relieve traction, and eliminate retinal ischaemia zones by performing panretinal photocoagulation (PRP).

Aim: The use of anti-VEGF therapy prior to vitrectomy for diabetic retinopathy remains a topic of debate. This study aims to evaluate whether pre-treatment with anti-VEGF offers clinical benefits.

Study Design: Prospective, randomised study

Place und Duration of Study: MSTC “Microsurgery of the eye”, Yekaterinburg city, Academician Bardina street 4a. Russian Federation, between 09/2022 and 05/2024.

Methodology: All patients were randomly assigned to one of three groups: Group 1: Underwent phacoemulsification and an injection of Ranibizumab, followed by vitrectomy, PRP, and silicone oil endotamponade one month later. Group 2: Received an intravitreal injection of 0.05 ml of Ranibizumab, followed 5–7 days later by phacoemulsification combined with vitrectomy, PRP, and silicone oil endotamponade. Group 3: Underwent phacoemulsification combined with vitrectomy, PRP, and silicone oil endotamponade, without prior intravitreal injection. Silicone oil was removed three months postoperatively. Clinical follow-up was conducted at 1 day, 3 months, and 6 months after surgery. The primary outcome measures were visual acuity and central retinal thickness, while secondary outcomes included the incidence of complications.

Results: The study included 113 patients with proliferative PDR in the advanced stages as classified by the ETDRS. The preoperative visual acuity was 0.04±0.02 in Group 1, 0.03±0.71 in Group 2, and 0.06±0.27 in Group 3. Central retinal thickness (CRT) was 512±9.4 µm in Group 1, 477±11.4 µm in Group 2, and 602±17.4 µm in Group 3. At the final follow-up, best-corrected visual acuity (BCVA) improved to 0.35±0.03 in Group 1, 0.41±0.03 in Group 2, and 0.22±0.07 in Group 3 (P ≤0,05). The minimum CRT at this stage was 294±19.4 µm in Group 1, 254±14.3 µm in Group 2, and 301±12.8 µm in Group 3 (P ≥0,05!). The incidence of complications at the final follow-up was as follows: retinal haemorrhage occurred in 2% of patients in both Groups 1 and 2, and 7% in Group 3 (P ≤0,05); haemophthalmos was observed in 0% of patients in Groups 1 and 2, but 9% in Group 3 (P ≤0,05); iris rubeosis occurred in 4% of patients in Group 1, 0% in Group 2, and 6% in Group 3; and tractional retinal detachment was reported in 11% of patients in Group 1, 4% in Group 2, and 19% in Group 3(P ≤0,05). Over the entire follow-up period, the overall complication rates were 30% in Group 1, 18% in Group 2, and 70% in Group 3 (P ≤0,05). The high incidence of haemorrhagic complications in Group 3 (22%) was statistically significant (P ≤0,05).

Conclusion: Preoperative administration of Ranibizumab at different intervals prior to surgical intervention statistically significantly improved both functional and anatomical outcomes in the treatment of PDR compared to sham treatment. The best functional and anatomical outcomes were observed in the group that received anti-VEGF injection five days before vitrectomy.

Recommendations: We recommend preoperative Ranibizumab before surgery. Both timings, 5 days and 30 days, give good results. In addition, we advise against vitrectomy without preoperative Ranibizumab.

Keywords: Angiogenesis inhibitors; proliferative diabetic retinopathy; phacoemulsification; vitreoretinal surgery.

1. INTRODUCTION

Currently, PDR and diabetic macular oedema DMO are recognised complications of DM and rank among the top five leading causes of blindness and visual impairment worldwide, including among working-age individuals (Yang et al., 2022; Golovin, 2024; Golovin, 2023; American Diabetes Association, 2019; Zang et al., 2022; Evgrafov & Kudasheva, 2022).

A hallmark of the long-term progression of DM in the vitreous cavity is the growth of newly formed blood vessels within the retinal tissue and optic disc, accompanied by the formation of FGT along the vitreoretinal interface in the posterior

segment of the eye fundus. This proliferative process extends deep into the vitreoretinal space, resulting in exudative-tractional changes in the central retina (Petrachkov et al., 2021; Van Geest et al., 2012).

The usual surgical approach for PDR with vitreoretinal traction is a vitrectomy. This surgical approach aims to restore optical media transparency, remove FGT, relieve traction, and eliminate retinal ischaemia zones by performing PRP (Golovin, 2023).

In contrast, to minimise the risk of haemorrhagic complications during the intra- and postoperative periods, as well as to address DMO, IVIs are widely employed in both the pre- and postoperative stages (Zamytsky et al., 2017; Akhmedova, 2021; Sharma et al., 2016; Arrigo et al., 2022; Evgrafov & Kudasheva, 2022; Li et al., 2022). The complexity of the pathogenetic mechanisms underlying PDR, the simultaneous involvement of the macular area and peripheral retina in surgical intervention, the risks of haemorrhagic complications, and the need for cataract surgery underscore the importance of investigating the optimal timing of angiogenesis inhibitors and cataract procedures in the combined treatment of PDR.

Concerns about increased retinal traction following anti-VEGF injections have led to their cautious use in preoperative settings. While some clinics avoid preoperative anti-VEGF therapy altogether, others adopt its use without hesitation (Arevalo et al., 2019; Bressler et al., 2020). This study seeks to determine whether the preoperative use of anti-VEGF has a positive or negative impact on surgical outcomes. Specifically, it evaluates whether a one-month interval after anti-VEGF injection results in increased retinal traction. With the inclusion of a control group, we also aim to compare complication rates across different approaches. Lastly, this study examines whether early cataract surgery offers additional benefits (Arevalo et al., 2019; Bressler et al., 2020).

2. PATIENTS AND METHODS

The study included 113 patients (113 eyes) aged 52 to 73 years (mean age 61±3.21), comprising 58% women and 42% men. Inclusion criteria were the presence of PDR in the advanced stages according to the ETDRS classification (levels 81 to 85) (Klein, 2007; Flaxman et al., 2017; Bikbov et al., 2019), combined with cataracts graded from the 2nd to 5th degree of density as per L. Buratto (Polyakova et al., 2016), and no history of angiogenesis inhibitor therapy or retinal laser photocoagulation within the past six months. Exclusion criteria included previous vitreoretinal surgeries and the presence of neovascular glaucoma.

Ophthalmological examinations at all stages of the study were conducted using: keratorefractometry (autokeratometer KR 8900, Topcon, Japan), visiometry (Topcon IS-600, Japan) with standard decimal optotypes, perimetry (PNA-002, Russia, Periscan), tonometry (iCare IC100, Finland Oy), ophthalmoscopy (Volk Digital Wide Field non-contact aspheric lens, USA), biomicro-ophthalmoscopy (SL 130, Carl Zeiss, Germany), optical coherence tomography (RTVue-100 XR, USA), and ultrasound B-scanning (UD-8000, Tomey, Japan). Photodocumentation of the ocular fundus (VISUCAM 500, Carl Zeiss, Japan) was performed for all patients, although preoperative photodocumentation was occasionally unavailable due to haemophthalmos.

All patients were randomly assigned to one of three groups based on the planned surgical treatment approach:

Group 1 (37 eyes): Phacoemulsification with an IVI of 0.05 ml of Ranibizumab, followed one month later (between 28 and 36 days, mean 30±2.34 days) by vitrectomy, PRP, and silicone oil (SO) endotamponade of the vitreal cavity. Silicone oil was removed after three months. If necessary, residual tractional retinal detachment was eliminated during the same session.

Group 2 (37 eyes): IVI of 0.05 ml of Ranibizumab, followed 5-7 days later by combined phacoemulsification and vitrectomy, PRP, and SO endotamponade of the vitreal cavity. SO was removed after three months. If necessary, residual tractional membranes were removed during the same session.

Group 3 (38 eyes): Combined phacoemulsification and vitrectomy, PRP, and SO endotamponade of the vitreal cavity without the use of angiogenesis inhibitors (IVI). SO was removed after three months. If necessary, residual tractional membranes were removed during the same session.

Surgical technique. Ranibizumab injections were administered using the standard technique, with

the injection placed 4 mm from the limbus and a dose of 0.5 mg/0.05 ml. During cataract surgery, intraocular lenses (IOLs) of various models were implanted using the standard procedure. The vitreoretinal intervention involved a 3-port vitrectomy, removal of fibrovascular membranes, PRP, and SO tamponade. The surgeries were carried out by experienced vitreoretinal surgeons, each with over 10 years of expertise in diabetic eye surgery. Intraoperative criteria by group included the average vitrectomy duration, use of a chandelier light, intraoperative use of perfluorocarbon, diathermocoagulator, and auxiliary dyes.

The PRP procedure involved full-volume application of laser spots (up to 1500 coagulations), with preliminary power testing to achieve a moderate intensity (Grade II according to L'Esperance F. classification) [5]. Retinal tears, if present, were also coagulated. In all cases, the vitreous cavity was tamponated with SO (Oxane 5700 or Alchimia RS-Oil 5000). Silicone oil was removed after three months. Any residual membranes, if present, were removed during the same session.

Anatomical and functional outcomes were assessed on the first day after surgery, and subsequently at 3 and 6 months of follow-up. Functional outcomes were analysed using BCVA and intraocular pressure (IOP), while anatomical outcomes were based on CRT. Additionally, complications occurring at all stages of follow-up were analysed, including inflammatory reactions, haemorrhagic complications, tractional retinal detachment, diabetic macular oedema, and rubeosis.

Statistical analysis of the study data was performed using Statistica v.10.0 software (StatSoft Inc., USA). The Kolmogorov-Smirnov test for normality was applied to determine the appropriate method for comparison and descriptive statistics. Since the majority of the sample data followed a normal distribution, the mean values and their standard error (M ± m) were calculated. To assess the significance of differences, the parametric criterion — two-sided Student's t-test — was employed. A critical significance level (p) of 0.05 was used for testing statistical hypotheses ($p < 0.05$).

3. RESULTS

3.1 Preoperative Data

The clinical characteristics of the observation groups are summarised in Table 1. The distribution of general and ocular characteristics was similar across all groups. As shown in Table 1, preoperative BCVA in all groups was below 0.1, primarily due to the presence of cataracts and haemophthalmos, which affected more than 30% of cases. Ophthalmoscopy was challenging in over 60% of the cases.

3.2 Surgical Data

Intraoperative features of the surgical treatment across the groups are presented in Table 2. No intraoperative complications were encountered during the surgical procedures.

Table 1. Characteristics of the observation groups at the preoperative stage

Group/Feature	Group 1	Group 2	Group 3
Diabetes History (years)	18±1.23	16±1.44	16±1.44
BCVA Before Surgery	0.04±0.02	0.03±0.71	0.06±0.27
CRT (μm)	512±9.4	477±11.4	602±17.4
Previously Performed PRP (More Than 6 Months Ago)	72%	77%	74%
Presence of Haemophthalmos Before Surgery	32%	40%	37%
Difficult Ophthalmoscopy	52%	61%	71%

Table 2. Features of intraoperative technique by groups

Group/Feature	Group 1	Group 2	Group 3
Average Vitrectomy Time (minutes)*	66±2.75	71±3.7**	82±2.62**
Diathermocoagulation (%)	82%	69%	77%
Chandelier (%)*	34%	29%	63%
Utilisation of Dyes (%)	11%	6%	24%
Perfluorcarbon Usage (%)	71%	59%	87%

**P ≤0,05*

*** — Total time (phaco + vitrectomy)*

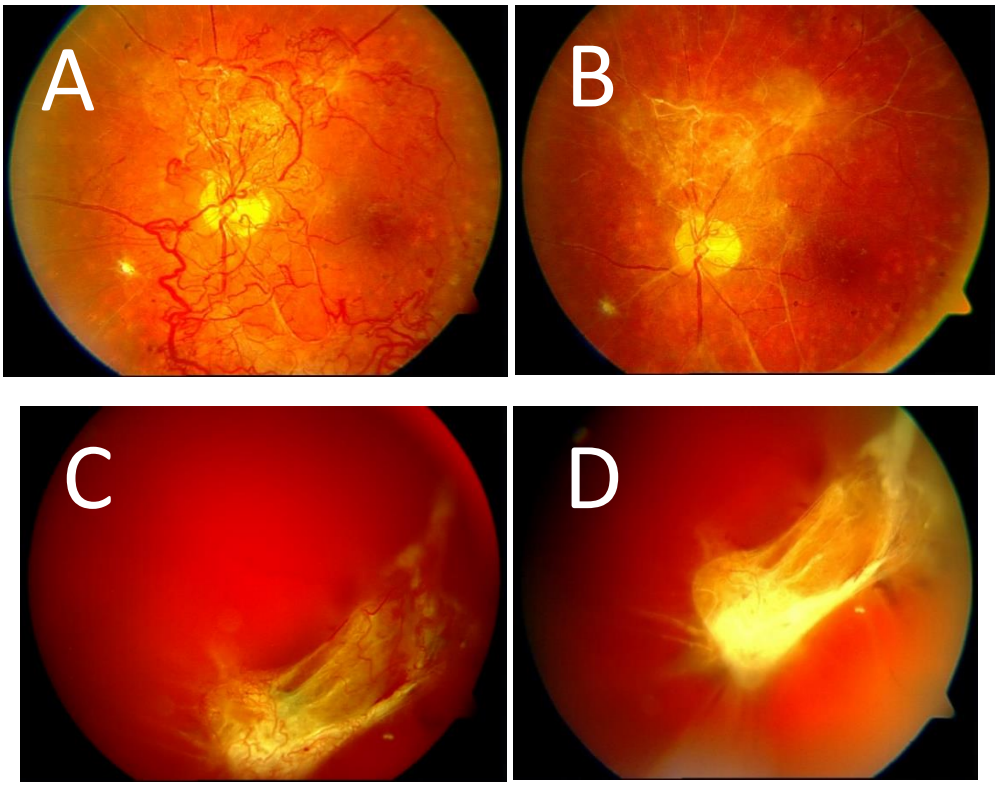

Fig. 1. Colour photograph of retinal traction before and after intravitreal Ranibizumab. A, C: Primary fundus. B: 1 month after intravitreal Ranibizumab. D. 5 days after intravitreal Ranibizumab. Note the closure of newly formed vessels

Based on the surgical data, the higher use of chandelier lighting in Group 3 was statistically significant, most likely due to surgeon preference, which may indirectly suggest the complexity of diabetic retinopathy surgery. The remaining parameters did not show statistically significant differences but demonstrated a similar distribution across the groups for subsequent analyses.

After 3 months, SO was removed from the vitreous cavity in 87% of cases, while in 13%, the tamponade period exceeded 6 months. The mean tamponade duration with silicone oil was 3.22±0.17 months in Group 1, 2.79±1.12 months in Group 2, and 3.42±0.42 months in Group 3, respectively.

3.3 Evaluation of Retinal Traction

Photodocumentation was performed before and after preoperative Ranibizumab administration. A comparison of colour photographs revealed no increase in retinal traction after 1 month, as compared to 5 days post-injection. In all cases available imaging revealed an obliteration of vessels, thinning and desiccation of fibrovascular membranes and reduction in the volume of haemorrhagic manifestations (haemophthalmos, intraretinal and preretinal haemorrhages).

4. POSTOPERATIVE COMPLICATIONS

The analysis of complications (Table 3) observed during the follow-up on the 1st day after surgical treatment revealed a statistically significant number of haemorrhagic complications in Group 3 (22%) when compared to Groups 1 and 2. Additionally, the statistically significant incidence of tractional retinal detachment before SO removal in Groups 1 (9%) and 3 (10%) is also noteworthy.

At the final follow up after 6 months, the most significant number of complications was observed in Group 3, including retinal haemorrhages (7%), delayed haemophthalmos (9%), iris rubeosis (6%), and tractional retinal detachment (19% in total). Other complications did not show statistically significant differences between the groups. The lowest total number of statistically significant postoperative complications was found in Group 2.

Table 3. Complications identified at all stages of follow-up (%)

Follow-up Period	1 Day Post-op.			3 Months (before SO removal)			6 Months (3 months after SO removal)		
Group Complications	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Retinal haemorrhages*	12%	3%	22%	1%	-	4%	2%	2%	7%
Haemophthalmos*	-	-	-	-	-	-	-	-	9%
Fibrin in the anterior chamber	-	1%	3%	-	-	-	-	-	-
Rubeosis*	-	-	-	-	-	-	4%	-	6%
Tractional retinal detachment*	-	-	-	9%	2%	10%	2%	2%	9%

**P ≤0,05*

Tractional retinal detachment reoccurred in some eyes after 3 and 6 months. After 3 months all cases of tractional retinal detachment were referred for reoperation. In each case, the surgical procedure involved SO removal, elimination of the formed membranes, additional laser photocoagulation of the retina, followed by tamponade with vitreous substitutes. Group 1: 2 cases of SO tamponade, 1 case of gas tamponade. Group 2: 1 case of perfluorocarbon tamponade with gas replacement after 1 week. Group 3: 1 case of perfluorocarbon tamponade with SO replacement after 1 week, 2 cases of SO tamponade, and 1 case of gas tamponade. All cases of tractional retinal detachment that occurred after 6 months were treated with fibrovascular membrane removal and silicone oil tamponade. After reoperation silicone oil had been removed in one case (*at the time of presentation of the study results) (in group 3).

5. POSTOPERATIVE OUTCOMES

The clinical options across the groups are presented in Table 4, which demonstrates an equal distribution of VA and CRT. Preoperative BCVA was below 0.1 in all groups. Based on the obtained data, IOP was within normal limits for all participants.

The best results ($p < 0.05$) over the entire follow-up period were observed in Group 2 (Ranibizumab followed by phacoemulsification and vitrectomy 5 days later), which exhibited the lowest CRT values ($p < 0.05$) and the best BCVA throughout the postoperative follow-up period. Group 2 was followed by Group 1 (one-time phacoemulsification and Ranibizumab, with vitrectomy after 1 month) in terms of both functional and anatomical results, demonstrating a significant improvement in visual acuity.

The results in Group 3 indicate that while visual and functional outcomes improved after vitrectomy, they were not as favourable as those in the groups receiving preoperative anti-VEGF treatment.

6. DISCUSSION

Preoperative administration of Ranibizumab at different intervals prior to surgical intervention statistically significantly improved both functional and anatomical outcomes in the treatment of PDR compared to sham treatment. The best functional and anatomical outcomes were observed in the group that received anti-VEGF injection five days before vitrectomy.

Table 4. Clinical and morphometric options during the entire follow-up period

Follow-up Period	Before Surgery			3 Months (before SO removal)			6 Months (3 months after SO removal)		
Group Criterion	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
BCVA*	0.04±0.02	0.03±0.71	0.06±0.27	0.23±0.06	0.33±0.6	0.15±0.4	0.35±0.03	0.41±0.03	0.22±0.07
IOP*	16.4±2.3	14.7±1.7	18.1±1.22	18.4±2.3	20.7±3.2	17.8±1.27	17.4±1.7	11.6±1.7	19.9±1.27
CRT (μm) (!)	512±9.4	477±11.4	602±17.4	302±12.4	284±24.3	317±11.8	294±19.4	254±14.3	301±12.8

**P ≤0,05*

(!) — presence of haemophthalmos before surgery: Group 1 — 32%; Group 2 — 40%; Group 3 — 37%; difficult ophthalmoscopy: Group 1 — 52%; Group 2 — 61%; Group 3 — 71%.

The findings of this study indicate that the use of angiogenesis inhibitors significantly improves both the anatomical and functional outcomes in the treatment of PDR, which is consistent with current clinical trial data (Gao et al., 2020; Smith & Steel, 2015; Zhao et al., 2018). A randomised study by Pei M. et al. (2023) demonstrated that the use of anti-VEGF therapy reduces the risks of intraoperative bleeding, iatrogenic retinal tears, the need for silicone tamponade, and the frequency of intraoperative diathermy. However, no statistically significant difference in postoperative visual acuity was observed (Pei et al., 2023).

In contrast, a multicentre study by Dervenis P. et al. (2023) reported a statistically significant improvement in visual acuity in the groups of patients receiving anti-VEGF during both the pre- and intraoperative periods, with these improvements sustained over a 6-month follow-up. This was also associated with a significantly lower risk of delayed haemophthalmos development. However, the remaining data did not demonstrate a high degree of certainty (Dervenis et al., 2023).

Besides, recent studies comparing different types of angiogenesis inhibitors have demonstrated their similar efficacy and safety profiles (Li et al., 2022).

In addition, the advancement of microsurgical techniques, coupled with the high risk of cataract development and progression following vitrectomy, has led to the introduction of combined (simultaneous) phacoemulsification and vitrectomy into clinical practice. The simultaneous performance of phaco and vitrectomy is further justified by the enhanced visualisation of the ocular fundus during surgery and in the postoperative period, as well as by the technical challenges associated with cataract removal in an eye without a vitreous body. This approach also reduces the rehabilitation period for patients and the total number of required surgical interventions. However, according to several authors (Golovin, 2024; Petrachkov et al., 2021), in patients with DMO and pre-existing damage to the haemato-ophthalmic barrier, such a surgical approach carries a high risk of postoperative complications, including secondary glaucoma, recurrence of haemophthalmos, uveitis, and diabetic macular oedema. A few studies investigating the efficacy of a two-stage approach — phacoemulsification followed by vitrectomy — compared to a one-stage phaco/vitrectomy procedure have suggested certain advantages of the former. However, the small number of observations prevented the authors from drawing definitive conclusions (Konovalova et al., 2020). In our study, the primary advantage of the two-stage approach was a shorter surgery time and less surgical trauma during vitrectomy, although these differences were not statistically significant. Moreover, cataract surgery, which is undoubtedly an aggravating factor in terms of intra- and postoperative trauma, can be effectively combined with a single vitreoretinal intervention, provided there is appropriate preparation with angiogenesis inhibitors (Groups 1 and 2).

The results of this study demonstrate that a 5-day interval between the injection of an angiogenesis inhibitor and combined PDR surgery is likely to have a sufficient effect on reducing haemorrhagic and possibly proliferative risks. This is consistent with earlier studies (Kalanov, 2018; Sabrosa, 2009; Shishkin & Yuldasheva, 2011; Faizrakhmanov et al., 2017; Konovalova et al., 2020; Raman et al., 2022; Gao et al., 2020; Smith & Steel, 2015; Zhao et al., 2018), as well as with the results observed in group 2, where minimal CRT and BCVA were achieved. However, special attention should be given to the peculiarities of group 2's randomisation, which may have influenced the findings. In this group, preoperative PRP was performed in 77% of cases, compared to 72% and 74% in groups 1 and 3, respectively. Furthermore, intraoperative features in Group 2 were characterised by slightly less surgical effort (as shown in Table 2), with the lowest percentage of chandelier and perfluorocarbon usage.

Equally noteworthy results were obtained in Group 1, which were nearly identical to those in Group 2, with the exception of a slightly higher incidence of haemorrhagic complications on the first day after surgery (12% of retinal haemorrhages), as well as cases of tractional detachment before SO removal. Group 1 also achieved comparable functional outcomes to Group 2 in terms of BCVA and CRT.

In any case, the combined treatment of proliferative diabetic retinopathy today necessitates the use of angiogenesis inhibitors as preoperative agents, as convincingly demonstrated by the high number of complications in Group 3.

It is also notable that more than 70% of patients had previously undergone PRP, a factor that can significantly influence the progression dynamics of PDR and the complexity of the surgical procedures performed.

In our view, the limitations of this study include the sample size and the complex nature of the clinical manifestations of PDR, which necessitate a multifactorial analysis. Each case of surgical treatment is unique, and factors such as the patients' overall medical status, glycated haemoglobin levels, and other laboratory parameters may directly influence both functional and anatomical outcomes. Undoubtedly, expanding the sample size would enhance the robustness of the findings.

Nevertheless, several current trends emerged during the course of this study, which can be succinctly summarised in the conclusions of the research.

7. CONCLUSIONS

Base on this study, it can be concluded as follows

1.Preoperative use of Ranibizumab statistically significantly improves both functional and anatomical outcomes in the treatment of PDR compared to sham treatment.
2.The best functional and anatomical outcomes were achieved in the group where the intravitreal injection of the angiogenesis inhibitor was administered 5 days prior to surgical treatment.

ETHICAL APPROVAL AND CONSENT

The study was performed in accordance with the Declaration of Helsinki on Research Involving Human Subjects and received approval from the local ethics committee. All patients were informed about the purpose and design of the study and provided written informed consent for the use of data obtained during the research.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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