Perioperative anti-vascular endothelial growth factor agents treatment in patients undergoing vitrectomy for complicated proliferative diabetic retinopathy: a network meta-analysis

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Currently, controversies regarding the optimal time-point of anti-vascular endothelial growth factor (VEGF) pretreatment before pars plana vitrectomy (PPV) for proliferative diabetic retinopathy (PDR) still exist. To clarify this, we conducted a network meta-analysis, 26 randomized controlled trials including 1806 PDR patients were included. Compared with the sham group, performing anti-VEGF injection at preoperative (Pre-Op) 6 to 14 days could significantly improve post-operative best-corrected visual acuity (BCVA) and decrease the incidence of recurrent vitreous hemorrhage (VH). Meanwhile, it could significantly reduce the duration of surgery. Performing anti-VEGF injection at Pre-Op more than 14 days, 6 to 14 days or 1 to 5 days could significantly reduce the incidence of intra-operative bleeding, while no significant benefit existed at the end of PPV ($P > 0.05$). No significant difference existed between all those strategies and sham group in reducing the rate of silicone oil tamponade. Based on currently available evidence, performing the anti-VEGF pretreatment at pre-operative 6 to 14 days showed best efficacy in improving post-operative BCVA, reducing the duration of surgery and incidence of recurrent VH, it also achieves satisfactory effect in reducing the incidence of intra-operative bleeding.

**Abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| 95% CI       | 95% Confidence interval |
| BCVA         | Best-corrected visual acuity |
| CS           | Complexity score |
| DR           | Diabetic retinopathy |
| ETDRS        | Early treatment diabetic retinopathy study |
| NVM          | Neovascular membrane |
| OR           | Odds ratio |
| PPV          | Pars Plana vitrectomy |
| PDR          | Proliferative diabetic retinopathy |
| Pre-Op       | Pre-operative |
| Post-Op      | Post-operative |
| RCT          | Randomized controlled trials |
| RD           | Retinal detachment |
| RNV          | Retinal neovascularization |
| Intra-Op     | Intra-operative |
| SMD          | Standardized mean difference |

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Despite the understanding and management of diabetes had evolved tremendously over the last decades, diabetic retinopathy (DR) is still one of the leading causes of legally blind and responsible for up to 4.8% of blindness globally. Proliferative diabetic retinopathy (PDR) is the worst stage of DR and always complicated with vitreous hemorrhage (VH) and even tractional retinal detachment (TRD). These complications are major causes of severe visual damage in PDR patients and need timely surgical interventions.

Pars plana vitrectomy (PPV) combined with anti-vascular endothelial growth factor (VEGF) agents injections had been widely accepted to be the standard management for PDR patients complicated with VH or TRD. Our previous meta-analysis had confirmed the pretreatment of anti-VEGF agents before vitrectomy for patients with complicated PDR might achieve much smoother surgery and better visual rehabilitation, reduce the rate of early recurrent VH and accelerate its absorption.

However, numerous controversies still exist and could not be solved by traditional randomized controlled trials (RCT) or meta-analysis. Firstly, the optimum time-point for the injection of anti-VEGF agents remains controversial. Current RCT or traditional meta-analysis could only conclude a pairwise comparison among these strategies. For instance, several RCTs reported that pre-operative anti-VEGF injection 5 to 10 days before PPV was clinically superior to 1 to 3 days, while no RCTs compared these time-points with anti-VEGF injection at the end of PPV or other time-points; Secondly, there are too many strategies for this anti-VEGF treatment reported by current studies, regarding different anti-VEGF agents, dosages and time-points.

The network meta-analysis is a new form of data synthesis, which could combine both the direct and indirect evidence of current RCTs using statistical techniques, yielding an estimate of comparative efficacy. Therefore, our network meta-analysis is performed to compare the efficacy of different perioperative time-points of anti-VEGF administration in patients undergoing PPV for complicated PDR, primarily looking at visual outcomes and recurrence of VH.

Method

This study was performed in accordance with the guidelines given by the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analysis (the ‘PRISMA’ statement).’

Search strategy. The PubMed, Embase and the Cochrane Central Register of Controlled Trials were searched up to March 2020 to identify relevant RCTs. The following keywords or corresponding Medical Subject Headings (Mesh) were used: ‘Diabetic Retinopathy’, ‘anti-VEGF’, ‘bevacizumab’, ‘ranibizumab’, ‘Randomized Controlled Trial’ and ‘Vitrectomy’. The detailed electronic search strategy of PubMed was (((((((((((((“Vascular Endothelial Growth Factors”[Mesh]) OR “KH902 fusion protein” [Supplementary Concept]) OR “aflibercept” [Supplementary Concept]) OR “Ranibizumab”[Mesh]) OR “Bevacizumab”[Mesh]) OR “pegaptanib” [Supplementary Concept]) OR Pegaptanib[Title/Abstract]) OR Bevacizumab[Title/Abstract]) OR Ranibizumab[Title/Abstract]) OR Aflibercept[Title/Abstract]) OR Conbercept[Title/Abstract]) OR Vascular Endothelial Growth Factors[Title/Abstract]) OR Macugen[Title/Abstract]) OR Avastin[Title/Abstract]) OR Lucentis[Title/Abstract]) OR Eylea[Title/Abstract]) OR anti-VEGF[Title/Abstract]) AND (((“Vitrectomy”[Mesh]) OR Vitrectomy[Title/Abstract]))) AND (((“random”[Title/Abstract]) OR “Randomized Controlled Trial” [Publication Type]))) AND (((“Diabetic Retinopathy”[Mesh]) OR (proliferative diabetic retinopathy[Title/Abstract]) OR RCT[Title/Abstract]))). The reference lists of the relevant articles were also manually examined to further identify potentially related RCTs. Only human studies published in English were considered.

Selection criteria. Inclusion criteria of our analysis were (1) participants: complicated PDR, defined as TRD or non-resolving VH requiring surgical intervention; (2) intervention: diabetic PPV; (3) comparison: different time-points or regimens of intravitreal injection of anti-VEGF agents; (4) outcomes: at least one of the followings: BCVA (log MAR scale); intraoperative parameters (including duration of surgery, intra-operative bleeding and silicone oil tamponade); postoperative parameters like recurrent VH; (5) Methodological criterion: RCTs.

Exclusion criteria were (1) patients with other intraocular diseases that may affect the vitreoretinal surgery, such as uveitis, proliferative vitreoretinopathy, retinal vascular disorders, congenital vitreoretinopathies and traumatic retinal detachment; (2) Other differences between case group and control group beside the application of anti-VEGF agents; (3) Insufficient data to estimate odds ratio (OR) or standardized mean difference (SMD); (4) animal studies or cadaver subjects; and (5) redundant publications.

Data extraction and quality assessment. After consecutive procedures of screening titles and abstracts, obtaining the full text of each article and reviewing them, articles that met the eligibility criteria and fail the exclusion criteria were included. Two authors (X-yZ and D-yW) independently extracted and collated data using a standardized data collection protocol. The extracted data included study characteristics (including first author, publication year, study duration and treatment allocation), patient characteristics (mean age, gender ratio, mean baseline BCVA), interventions (anti-VEGF groups, intervention doses and usage), details of the surgical procedure, outcomes (change in BCVA, and postoperative evaluating parameters) and follow-up period.
For updated publications with the same cohort of patients of the previous study, the data was extracted only once. The corresponding authors of the included articles would be contacted if the essential data were unavailable. Discrepancies were evaluated by kappa text and agreement was achieved by consensus. The Cochrane risk of bias assessment tool was used to assess the methodological quality and risk of bias.

Outcomes. The primary outcomes of interest were the post-operative best-corrected visual acuity (BCVA) at the final follow-up and the incidence of recurrent vitreous hemorrhage (VH). Secondary outcomes were the duration of surgery, the incidence of silicone oil tamponade and intra-operative bleeding.

Data synthesis and statistical analysis. We separately used SMD for continuous outcomes and OR for dichotomous outcomes. The network meta-analysis was conducted with indirect and mixed comparisons in Stata version 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) through the mvmeta command, network command and self-programmed Stata routines. Cochran Q test and the I² statistic were applied to assess the heterogeneity. We use global inconsistency test by fitting design-by-treatment in the inconsistency model to evaluate the level of heterogeneity between direct and indirect estimates. The local inconsistency was assessed using node-splitting method. The loop-specific approach which assesses the difference between direct and indirect estimates for a specific comparison in the loop was also applied to check the inconsistency. If the results of these inconsistency tests were acceptable (P > 0.05), the consistency model would be selected to compare all the regimens using direct and indirect data. The rankograms, surface under the cumulative ranking (SUCRA) curves and the mean ranks were estimated to rank the intervention hierarchy of competing regimens in the network meta-analysis. The higher SUCRA potentially represents superior efficacy. The publication bias of each outcome was clarified by the comparison-adjusted funnel plot. When heterogeneity or inconsistency was found substantial in any outcome (P < 0.05), both sensitivity analysis and subgroup analyses (publication year, sample size, etc.) would be conducted to identify the source of the heterogeneity. If the heterogeneity or inconsistency could not be eliminated, the pooling result of this specific outcome would be regarded as invalid.

Results

Study characteristics. We identified 212 citations by the initial search, then 32 potentially eligible articles were retrieved in full text after reviewing the titles and abstracts. Of these studies, 6 reports were excluded for irrelevant or insufficient data. Finally, 26 studies including 1802 PDR patients were included in our study, the detailed literature-exclusion procedures were described in Fig. 1. The inter-rater agreement was excellent between the investigators regarding eligibility (k = 0.79). The main characteristics of these included studies were presented in Table 1. Five nodes regarding the timing of the anti-VEGF injection were included in our network meta-analysis, including pre-operative (Pre-Op) more than 14 days, 6 to 14 days, 1 to 5 days, at the end of PPV and sham injection (Fig. 2). In general, most of these studies (25 of 26) were judged to have an unclear risk of bias (Suppl. 1, 2), none of these studies had evidence of a definite high risk in any item.

Primary outcomes. The network diagrams of all eligible comparisons for the primary outcomes are presented in Fig. 2 and the results of network meta-analysis were shown in Fig. 3. The mean ranking based on SUCRA curves of the primary outcomes were shown in Table 2, a higher SUCRA potentially means superior efficacy. The detailed results of head-to-head comparisons were provided in Table 3. Thirteen RCTs involving 889 patients provide adequate data for the primary outcome of post-operative BCVA and incidence of recurrent VH, the most effective time-point was estimated to be Pre-Op 6 to 14 days (Table 2). Compared with the sham group, performing anti-VEGF injection at Pre-Op 6 to 14 days could significantly improve post-operative BCVA (SMDs = −0.43, 95% credible interval [CI]: −0.85 to −0.01, P < 0.05, Fig. 3) and decrease the incidence of recurrent VH (OR = 2.25, 95% CI: 1.01 to 1.19, P < 0.05). Meanwhile, performing the anti-VEGF injection at the other three time-points could also significantly reduce the incidence of recurrent VH (P < 0.05), while no significant difference existed for post-operative BCVA when compared with the sham group (P > 0.05).

Secondary outcomes. The results of network meta-analysis were shown in Fig. 4. The corresponding mean ranking based on SUCRA curves was also listed in Table 2, a higher SUCRA potentially means superior efficacy. For all the secondary outcomes, detailed results of head-to-head comparisons were provided in Suppl. 1, 3, 4, 5. Eleven RCTs involving 762 patients reported the duration of surgery and Pre-Op 6 to 14 days was estimated to be the most effective strategy (Table 2). Compared with the sham group, Pre-Op 6 to 14 days could significantly reduce the duration of surgery (SMDs = −0.60, 95% CI: −1.21 to −0.01, P < 0.05, Fig. 4), while no statistical difference existed between other time-points (P > 0.05). Ten RCTs involving 715 patients describe the rate of silicone oil tamponade, Pre-Op more than 14 days was estimated to have the highest SUCRA ranking (Table 2), while there was no significant difference between all those strategies and sham group (P > 0.05, Fig. 4). Eleven RCTs involving 791 patients evaluated the incidence of intra-operative bleeding. The network meta-analysis showed that Pre-Op more than 14 days achieved the highest SUCRA ranking (Table 2). Compared with the sham group, performing anti-VEGF injection at Pre-Op more than 14 days, 6 to 14 days or 1 to 5 days could significantly reduce the incidence of intra-operative bleeding (P < 0.05, Fig. 4), while conducting anti-VEGF injection at the end of PPV could not achieve any significant benefit (P > 0.05).
Subgroup analysis. The subgroup SUCRA analysis was then conducted regarding the detailed interventions in each study, including different agents, dosages and time-points. The corresponding mean ranking based on SUCRA curves was listed in Table 4.

Inconsistency and heterogeneity. Global inconsistency, local inconsistency or heterogeneity were not significant between evidence derived from direct and indirect comparisons in both of the primary and secondary outcomes (P > 0.05). The corresponding comparison-adjusted funnel plots also showed no evidence of asymmetry (P > 0.05).

Discussion
This analysis is a comprehensive network meta-analysis in evaluating the efficacy of different time-points of perioperative anti-VEGF injection for patients undergoing vitrectomy for complicated PDR. The results of our study indicated that anti-VEGF injection at pre-operative 6 to 14 days showed the best efficacy in improving post-operative BCVA, reducing the duration of surgery and incidence of recurrent VH, it also achieves satisfactory effect in reducing the incidence of intra-operative bleeding. Additionally, the general efficacy ranking of each detailed regimen was achieved for reference. More importantly, our study provides a solid reference for the current most concerned controversies mentioned in the introduction.

The purpose of perioperative anti-VEGF injection is to induce the regression of retinal neovascularization (RNV), decrease the intra-operative bleeding, and facilitate easier fibrovascular membrane dissection and smoother vitreoretinal surgery. Some authors suggested performing the injection with an interval of more than 14 days,[20,21] in order to make full use of anti-VEGF agents and induce the complete regression of RNV. While other expressed their concerns about the formation or aggravation of tractional retinal detachment (TRD) associated with progressive fibrosis of fibrovascular membrane following the pretreatment of anti-VEGF agents[22,23], so they suggested performing the injection with a short interval like 1 to 3 days.[6,24] Russo et al.[25] studied the incidence of tractional macular detachment following pre-vitrectomy anti-VEGF injection and showed that a longer period between the injection and the surgery increases the incidence of tractional macular detachment; in particular, when anti-VEGF injection was given within 6 days from PPV, tractional macular detachment happened in 2.7% of cases, when the injection was given more than 10 days before vitrectomy, rate of TMD increased to 56%.

For the postoperative BCVA, numerous factors might be associated with it, like the history of TRD, surgical trauma, recurrent VH, silicone oil tamponade, diabetic macular edema. Although it was “barely” significant
| First author            | Year | Study location | Design | Participants | Intervention | Group size | Average age | Sex (M/F) | Outcomes                                                                 | Follow-up |
|------------------------|------|----------------|--------|--------------|--------------|------------|-------------|-----------|---------------------------------------------------------------------------|-----------|
| Rizzo et al.           | 2007 | US             | RCT    | PDR          | IVB, 1.25 mg, pre-Op 5–7 days versus Sham | 11/11      | 22          | NA        | Complexity score, main-feasibility of surgery, BCVA                      | 6 months  |
| Pakzad-Vaezi et al.    | 2014 | UK             | RCT    | PDR          | IVB, 1.25 mg/0.05 mL versus IVB, 0.50 mg/0.05 mL | 15/14      | 29          | 52.5      | Total surgical time, TRD, Intra-operative bleeding, iatrogenic retinal breaks, use of endolaser and endodiat hermy, silicone oil | In operation |
| Castillo et al.        | 2017 | Mex            | RCT    | PDR          | IVB, 2.5 mg/0.1 mL, pre-Op 1–3 days versus IVB, 2.5 mg/0.1 mL, pre-Op 5–10 days | 73/65      | 126         | 54.9/57.4 | BCVA, Intraoperative surgery time, Intra-operative complications, post-operative complications | 6 months  |
| Arevalo et al.         | 2019 | 9 countries    | RCT    | PDR          | IVB, 1.25 mg/0.1 mL, pre-Op 3–5 days versus Sham | 102/112    | 224         | 59.5 ± 11.0/61.3 ± 10 | 116/68 | Intraoperative bleeding, total surgical time, early postoperative VH, BCVA, endodiathermy applications, intraoperative retinal breaks, change in central macular thickness | 12 months |
| Ahmadih et al.         | 2009 | Iran           | RCT    | PDR          | IVB, 1.25 mg/0.05 mL, pre-Op 7 days versus sham | 35/33      | 68          | 55.2 ± 11.1 | Incidence of early post-vitrectomy hemorrhage, BCVA, IVB-related adverse events | 1 months  |
| Yang et al.            | 2015 | China          | RCT    | PDR          | IVC, 0.5 mg/0.05 mL, pre-Op 3 days versus sham | 54/53      | 107         | 48.63/49.64 | Intraoperative bleeding, VH, BCVA, TRD, IOP, Endophthalmitis, Rubeosis, adverse events | 3 months  |
| Ahn et al.             | 2011 | Korea          | RCT    | PDR          | IVB, 1.25 mg/0.05 mL, pre-Op 1 to 14 days before PPV versus IVB, 1.25 mg/0.05 mL at the end of PPV versus sham | 36/37/34   | 107         | NA        | VH, time of vitreous clearing, BCVA                                     | 6 months  |

Continued
| First author | Year | Study location | Design | Participants | Intervention | Group size | Average age | Sex (M/F) | Outcomes | Follow-up |
|--------------|------|----------------|--------|--------------|-------------|------------|-------------|-----------|----------|-----------|
| Lauro et al. | 2009 | Italy          | RCT    | PDR          | IVB, 1.25 mg/0.1 mL, pre-Op 7 days versus IVB, 1.25 mg/0.1 mL, pre-Op 20 days versus Sham | 24/24/24 | 72 | NA | NA | 6 months |
| Modarres et al. | 2009 | Iran           | RCT    | PDR          | IVB, 2.5 mg/0.1 mL, pre-Op 3–5 days versus sham | 22/18 | 40 | 5.8 ± 11.3/53.2 ± 11.7 | NA | 7 ± 3.6 months |
| Hernández-Da Mota et al. | 2010 | Mex            | RCT    | PDR          | IVB, 1.25 mg/0.1 mL, pre-Op 2 days versus sham | 20/20 | 40 | 55.7 ± 7.4/ 55.7 ± 9.9 | 24/16 | 6 months |
| Han et al. | 2012 | China          | RCT    | PDR          | IVB, 1.25 mg, pre-Op 2 days versus sham | 12/12 | 24 | 50.3/53.25 | 12/12 | NA |
| Farahvash et al. | 2011 | Iran           | RCT?   | PDR          | IVB, 1.25 mg/0.05 mL, pre-Op 7 days versus sham | 18/17 | 35 | 58.5 | 18/17 | 7 months |
| Aleman et al. | 2019 | US             | RCT    | PDR          | IVZ, 1.25 mg/0.05 mL, pre-Op 1–10 days versus IVB 1.25 mg/0.5 mL, pre-Op 1–10 days | 82/91 | 206 | 58/55.8 | 91/82 | 6 months |
| Velazquez et al. | 2018 | Mex            | RCT    | PDR          | A: IVB 0.625 mg/0.025 mL, pre-Op 1–10 days; B: IVB 1.25 mg/0.05 mL, pre-Op 1–10 days; C: IVB 2.5 mg/0.1 mL, pre-Op 1–10 days | 75/59/72 | 206 | 57.3/55.6/56.3 | 74/93 | 6 months |

Continued
| First author | Year | Study location | Design | Participants | Intervention | Group size | Average age | Sex (M/F) | Outcomes | Follow-up |
|--------------|------|----------------|--------|--------------|-------------|------------|-------------|-----------|----------|-----------|
| Comyn et al. | 2017 | UK | RCT | PDR | IVR, 0.5 mg/0.05 mL, pre-Op 7 days versus Sham | 15/15 | 30 | 48.7/57.1 | 18/12 | ETDRS BCVA, extend of TRD and Macular perfusion, surgery Time, surgery instrument usage, intraoperative haemorrhage, postoperative vitreous cavity haemorrhage | 3 months |
| Hattori et al. | 2010 | Japan | RCT | PDR | IVB, 0.5 ± 0.39 (0.16–1.25), pre-Op 3 days versus Sham | 12/40 | 52 | 59.1 ± 9.4 | NA | VEGF concentration, Numbers of intraoperative coagulation spots | NA |
| Manabe et al. | 2015 | Japan | RCT | PDR | IVB, 0.16 mg/0.05 mL, pre-Op 1 day versus sham | 32/34 | 66 | 59.9 ± 11.8/59.2 ± 12.9 | 54/12 | VH, numbers of intraoperative laser, endo-diathermy, concentration of VEGF | 1 months |
| Su et al. | 2016 | China | RCT | PDR | IVC, 0.5 mg/0.05 mL, pre-Op 7 days versus sham | 18/18 | 36 | NA | NA | BCVA, intraoperative bleeding, Endo-diathermy, Iatrogenic break, Silicone oil, Surgical mean time | 6 weeks |
| Zaman et al. | 2013 | Pakistan | RCT | PDR | IVB, 1.25 mg/0.05 mL, pre-Op 7 days versus sham | 30/24 | 54 | 52.07 ± 5.54 | 32/22 | BCVA, postoperative complication, VH | 6 months |
| Jeon et al. | 2012 | Korea | RCT | PDR | IVB, 1.25 mg/0.05 mL, pre-Op 1-day versus IVB 1.25 mg/0.05 mL, pre-Op 7 days | 15/15 | 30 | 58.71 ± 9.77/55.83 ± 10.67 | 19/11 | VEGF, IL-6, IL-8, TGF-β2, IL-2, TNF-α | 1 day |
| Li et al. | 2015 | China | RCT | PDR | IVB, 1.25 mg/0.05 mL, pre-Op 5 days versus IVB, 1.25 mg/0.05 mL, pre-Op >14 days versus Sham | 23/11/19 | 68 | 48.9 ± 11.2/53.9 ± 8.5 | 29/24 | Vitreous VEGF, bFGF, fibrosis | NA |
| Lucena et al. | 2009 | USA | RCT | PDR | IVB 1.25 mg/0.05 mL, pre-Op 14 days versus sham | 10/10 | 20 | NA | 10/10 | Amount of intraocular haemorrhage, | NA |
| Zhou et al. | 2018 | China | RCT | PDR | IVC, 0.5 mg, pre-Op 7 days versus sham | 9/9 | 16 | 51.69 ± 8.5 | 14/11 | BCVA, VEGF, PIGF | 3 months |
| Li et al. | 2020 | China | RCT | PDR | IVC, 0.5 mg/0.05 mL, pre-Op 7 days versus IVC, 0.5 mg/0.05 mL, pre-Op 14 days versus sham | 20/20/20 | 60 | 50.6 ± 5.6 | 32/28 | CS, intraoperative bleeding, VEGF concentrations, total surgical time | NA |

Continued
(SMDs = −0.43, 95% CI: −0.85 to −0.01), the pooling results of our study indicated that only performing anti-VEGF injection at Pre-Op 6 to 14 days could significantly improve post-operative BCV A compared with the sham group, which were also supported by the corresponding head-to-head comparisons21. So was the duration of surgery, only performing the injection at Pre-Op 6 to 14 days could significantly reduce the operative time compared with the sham group, which might mean easier and smoother surgery. While our study showed that these pretreatments could not significantly reduce the incidence of silicone oil tamponade, which is standard procedure for TRD and last resort for unstoppable intra-operative bleeding.

Routinely diabetic PPV without anti-VEGF pretreatment was always troublesome by intra-operative bleeding. Firstly, hemorrhages make it difficult to perform the delamination and segmentation of the fibrovascular tissue, they usually adhere tightly to retina surface, the removal of these tissues has high risk of iatrogenic retinal breaks26; Secondly, continued intra-operative bleeding may impede adequate endophotocoagulation as poor visualization, increasing the risk of rubeosis iridis and subsequently neovascular glaucoma after surgery; Additionally, difficult-to-control bleeding during surgery wastes plenty of time, which might cause other complications like

| First author | Year | Study location | Design | Participants | Intervention | Group size | Average age | Sex (M/F) | Outcomes | Follow-up |
|--------------|------|----------------|--------|--------------|-------------|------------|-------------|-----------|----------|-----------|
| Gao et al.   | 2020 | China          | RCT    | PDR          | IVC, 0.5 mg/0.05 mL, pre-Op 3–5 days versus IVC, 0.5 mg/0.05 mL, end of surgery | 34/35       | 69          | 50.76 ± 13.47/53.97 ± 14.76 | 30/39 | BCVA, IOP, intraoperative bleeding, surgery duration, postoperative follow-up | 6 months |
| Cui et al.   | 2018 | China          | RCT    | PDR          | IVC, 0.5 mg/0.05 mL, pre-Op 3–7 days versus IVR, 0.5 mg/0.05 mL, pre-Op 3–7 days | 20/19       | 39          | 60.74 ± 2.63/55.28 ± 5.16 | 24/15 | BCVA, operation time, incidence of iatrogenic retinal breaks, endodiaterymy rate, and silicone oil tamponade, vitreous clearing time, intraoperative and postoperative bleeding | 6 months |

Table 1. Main characteristics of the included studies. BCVA best corrected visual acuity, CS complexity score, IOP intraocular pressure, IVB intravitreal injection of Bevacizumab, IVC intravitreal injection of conbercept, IVR intravitreal injection of ranibizumab, NVM neovascular membrane, NA not available, PDR photodynamic therapy, RCT randomized controlled trial, TRD tractional retinal detachment, VEGF vascular endothelial growth factor, VH vitreous hemorrhage.
corneal opacification and poor visualization of the surgical field, all these may result in poor surgical outcome. Our studies showed that pretreatment of anti-VEGF could all significantly reduce the incidence of intra-operative bleeding, Pre-Op more than 14 days achieved the highest SUCRA ranking, while conducting anti-VEGF injection at the end of PPV could not achieve any beneficial effect. It is understandable as anti-VEGF agents need time to take effect, longer interval equals to better regression of NV and absorption of hemorrhages.

Recurrent VH after PPV for PDR is the major concern for both patients and surgeons, with a reported incidence up to 75%28. It might greatly jeopardize patient’s expectations, prevents clear fundus examination and further laser therapy. The source of early and late postoperative recurrent VH were different, early recurrent VH was associated with dissection of fibrovascular membranes, recurrent bleeding from initial bleeding site, surgically injured retinal tissue and increased vascular permeability5,6 while recurrent neovascularization was believed to be the crucial cause in late recurrent VH and RD29. The pooling results of our study indicated that performing the anti-VEGF injection at all the four time-points could achieve a significantly lower incidence of recurrent VH.

Table 2. The estimated mean ranking based on surface under the cumulative ranking (SUCRA) curves of all primary and secondary outcomes in the network meta-analysis. A higher SUCRA potentially means superior efficacy or safety. BCVA best-corrected visual acuity, Pre-Op pre-operative, PPV pars plana vitrectomy, SUCRA surface under the cumulative ranking.

| Ranking | Post-Op BCVA | Duration of surgery | Recurrent VH | Silicone oil tamponade | Intra-Op bleeding | SUCRA |
|---------|--------------|---------------------|--------------|------------------------|------------------|--------|
| Best    | Pre-Op 6 to 14 days | 80.3 | Pre-Op 6 to 14 days | 83.7 | Pre-Op 6 to 14 days | 90.9 | 82.9 | 79.2 |
| 2nd     | Pre-Op 1 to 5 days | 64 | Pre-Op more than 14 days | 76.2 | At the end of PPV | 56.2 | 60.5 | 74.6 |
| 3rd     | Pre-Op more than 14 days | 59.1 | Pre-Op 1 to 5 days | 40.5 | Pre-Op more than 14 days | 55.4 | 38.3 | 55.5 |
| 4th     | At the end of PPV | 23.4 | Sham | 39.7 | Pre-Op 1 to 5 days | 44.1 | At the end of PPV | 39 | 27.5 |
| 5th     | Sham | 23.2 | At the end of PPV | 10 | Sham | 3.4 | Pre-Op 1 to 5 days | 29.4 | 13.4 |

Table 3. Head-to-head comparisons for primary outcomes of different time-points of perioperative anti-VEGF treatment. The bold items mean *P* < 0.05. 95% CI 95% confidence interval, BCVA best-corrected visual acuity, OR odds risk, Pre-Op pre-operative, PPV pars plana vitrectomy, SMD standardized mean difference, VEGF vascular endothelial growth factor, VH vitreous hemorrhage.
Recently, anti-VEGF agents were used to delay VEGF-related late ischemia in the retina, leading to the prevention of recurrent VH. Fifty-eight articles related to anti-VEGF agents were included in the meta-analysis; 27 were RCTs. Recurrent VH compared with the sham group, also leading by Pre-Op 6 to 14 days. However, anti-VEGF agents could only provide complete VEGF blockade for about 4 weeks and almost all the amount of anti-VEGF agents injected preoperatively would be removed during vitrectomy, panretinal photocoagulation should be done adequately during and post-surgery to prevent recurrent neovascularization and reduce the incidence of late recurrent VH and postoperative recurrent RD.

Our study still has several limitations. (1) Our findings are achieved through direct and indirect comparisons in a network meta-analysis. Although this method is widely accepted with better statistical precision, it could not substitute results from large-scale RCTs; (2) Although we conducted the subgroup analysis regarding different agents, dosages and time-points, they included too many different regimens and it was difficult to achieve an universally applicable conclusion, the results might just give some hints like a higher dosage of anti-VEGF could achieve better outcomes than traditional dosage; (3) Only RCTs published in English were considered.

Table 4. The estimated mean ranking based on surface under the cumulative ranking (SUCRA) curves of the subgroup analysis. Italic means the data was unobtainable or could not be included in the main closed loop; A higher SUCRA potentially means superior efficacy or safety. BCVA best-corrected visual acuity, IVB intravitreal injection of Bevacizumab, IVC intravitreal injection of conbercept, IVR intravitreal injection of ranibizumab, NA not available, Pre-Op pre-operative, Post-Op post-operative, PPV pars plana vitrectomy, SUCRA surface under the cumulative ranking, VH vitreous hemorrhage.

| Ranking | Post-Op BCVA | SUCRA | Duration of surgery | SUCRA | Recurrent VH | SUCRA | Silicone oil tamponade | SUCRA | Intra-Op bleeding | SUCRA |
|---------|--------------|-------|---------------------|-------|--------------|-------|---------------------|-------|---------------------|-------|
| Best    | IVB, 2.5 mg, 6–14 days | 91.9  | IVC, 0.5 mg, 6–14 days | 83.8  | IVB, 2.5 mg, 6–14 days | 88.1  | IVB, 1.25 mg, 6–14 days | 75.4  | IVB, 2.5 mg, 1–5 days | 72.9  |
| 2nd     | IVB, 2.5 mg, 1–5 d | 81.2  | IVB, 1.25 mg, 6–14 days | 71.5  | IVB, 2.5 mg, 1–5 days | 73.5  | IVB, 1.25 mg, 6–14 days | 62.4  | IVB, 1.25 mg, > 14 days | 65.3  |
| 3rd     | IVC, 0.5 mg, 6–14 d | 57.6  | IVB, 1.25 mg, 6–14 days | 70.1  | IVB, 1.25 mg, 1–5 days | 62.1  | IVB, 1.25 mg, 6–14 days | 61.6  | IVC, 0.5 mg, 6–14 days | 62.8  |
| 4th     | IVC, 0.5 mg, 1–5 days | 54.5  | IVB, 1.25 mg, 6–14 days | 68.3  | IVC, 0.5 mg, 1–5 days | 59.7  | IVC, 1.25 mg, at the end of PPV | 50.5  | IVC, 0.5 mg, 1–5 days | 57.9  |
| 5th     | IVB, 1.25 mg, 6–14 days | 51.5  | IVB, 2.5 mg, 6–14 days | 53.2  | IVC, 0.5 mg, 1–5 days | 46.1  | IVB, 0.5 mg, 1–5 days | 50.4  | IVC, 0.5 mg, 7–14 days | 57.2  |
| 6th     | IVC, 0.5 mg, at end of PPV | 48.7  | IVB, 0.5 mg, 7–14 days | 49.8  | IVB, 1.25 mg, 6–14 days | 43.6  | IVB, 1.25 mg, at the end of PPV | 34.4  | IVC, 0.5 mg, 1–5 days | 47.2  |
| 7th     | IVB, 1.25 mg, > 14 days | 45.6  | IVB, 2.5 mg, 1–5 days | 48.2  | IVB, 1.25 mg, at the end of PPV | 34.4  | IVB, 1.25 mg, 1–5 days | 45.5  | IVC, 0.5 mg, 1–5 days | 47.2  |
| 8th     | IVB, 1.25 mg, 1–5 days | 35.3  | Sham | 45.3  | IVB, 1.25 mg, 1–5 days | 29.5  | IVC, 0.5 mg, at the end of PPV | 37.8  | IVC, 0.5 mg, at the end of PPV | 37.4  |
| 9th     | IVR, 0.5 mg, 1–5 days | 34.7  | IVB, 0.5 mg, 1–5 days | 31.2  | Sham | 13  | IVB, 0.5 mg, 1–5 days | 34.9  | IVC, 0.5 mg, 1–5 days | 26.3  |
| 10th    | Sham | 29.9  | IVC, 0.5 mg, 1–5 days | 20.8  | IVB, 0.5 mg, 1–5 days | NA  | IVC, 0.5 mg, 1–5 days | 32.2  | Sham | 17.8  |
| 11th    | IVB, 1.25 mg, at the end of PPV | 19  | IVB, 0.5 mg, 1–5 days | 7.8  | IVC, 0.5 mg, 6–14 days | NA  | IVB, 2.5 mg, 6–14 days | NA  | NA  | NA  |
| 12th    | IVC, 0.5 mg, 7–14 days | NA  | NA  | IVC, 0.5 mg, 7–14 days | NA  | NA  | IVC, 0.5 mg, 7–14 days | NA  | NA  | NA  |

Figure 4. Network meta-analysis of different time-points of perioperative anti-VEGF treatment compared with sham treatment for the secondary outcomes: (A) Duration of surgery; (B) Rate of silicone oil tamponade; (C) Incidence of intra-operative bleeding. Pre-Op pre-operative, PPV pars plana vitrectomy.
Conclusion
In summary, our study suggests that performing the anti-VEGF pretreatment at pre-operative 6 to 14 days showed the best efficacy in improving post-operative BCVA, reducing the duration of surgery and incidence of recurrent VH, it also achieves satisfactory effect in reducing the incidence of intra-operative bleeding.

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Author contributions
D.W. carried out the entire procedure including the literature search, data extraction and drafted the manuscript. W.Z. and L.M. revised the manuscript. X.Z. and Y.C. conceived of the study, coordinated and participated in the entire process of drafting and reviewing the manuscript.

Competing interests
The authors declare no competing interests.
