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META-ANALYSIS

Appropriate timing schedule for intravitreal anti-VEGF injection as adjuvant therapy before pars-plana vitrectomy in proliferative diabetic retinopathy, a meta analysis

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ABSTRACT

Background: Many studies introduced intravitreal injections of anti-vascular endothelial growth factors (VEGFs) as a new strategy for safer and more convenient vitrectomy in patients with severe proliferative diabetic retinopathy (PDR). While possible side effects such as progression of vitreoretinal fibrosis should be kept in mind, these may be prevented by proper preoperative timing of injection.

Research design and methods: This study was conducted based on the systematic review guidelines in four steps: definition of search strategy, selecting and evaluating studies, checking inclusion and exclusion criteria, and statistical analysis. Eighteen clinical trials with a total sample size of 1165 patients were included. According to the timing of injection, patients were divided into three groups: injection 72 hours, injection 3–7 days, and injection 7–21 days before surgery.

Results: The lowest risk of intraoperative hemorrhage, the minimum duration of surgery and the lowest need for silicone oil (SO) tamponade was in the injection group 7–21 days before surgery. The rate of iatrogenic retinal break during surgery and the necessity for relaxing retinotomy in the injection group 72 hours before surgery was lower than the other two groups. However, there were limited data regarding the requirement of relaxing retinotomy, the need to inject SO, and the occurrence of iatrogenic retinal break.

Conclusions: This meta-analysis showed, to prevent tractional complications, it is recommended to inject within 3 days before surgery.

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Diabetic retinopathy; Proliferative diabetic retinopathy; Vitrectomy; Pars-plana vitrectomy; PPV; Anti-VEGF; Vascular endothelial growth factor

1. Introduction

The epidemic of diabetes mellitus (DM) has become an emerging public health concern in recent years, and an estimated 642 million people affected worldwide by 2040 [1]. Diabetic retinopathy (DR) is the commonest cause of irreversible visual loss at a working age worldwide and proliferative diabetic retinopathy (PDR) is the prevalent cause of blindness among these patients. Despite recent developments in ophthalmology, there are no proven preventive proceedings for DR unless tight control of DM. However, emerging therapeutic strategies in the last decades have effectively prevented progressive vision loss.

Previous reports introduced vascular endothelial growth factor (VEGF) as a pivotal causative agent in pathologic ocular neovascularization or increased vascular permeability, such as diabetic macular edema (DME) and PDR, which are common causes of visual impairment in diabetic patients [2]. Latter often resulting in vision loss because of critical complications such as ischemic induced neovascularization, vitreous hemorrhage, and subsequently tractional retinal detachment (TRD) [3]. Also the incidence of DME in patients with severe PDR is up to 70% [4]. In severe PDR and its complications, pars-plana vitrectomy (PPV) may be the most effective treatment to save vision and introduced as mainstay procedure which removes fibrovascular membranes and vitreoretinal traction [5]. During PPV in these patients, vitreous cavity hemorrhage when dissecting fibrovascular membranes will significantly restrict visualization of the surgical field which can prolong the surgery time, increase the frequency of instrument exchange, and seriously increase the rate of complications.

Recently, many studies confirmed the effectiveness of preoperative intravitreal anti-VEGF therapy, which is believed reduces many surgical procedures and complications. Four applied anti-VEGF monoclonal antibodies have been evolved and verified in patients with PDR, such as Bevacizumab (Avastin; Genentech Inc., CA), Conbarcept (Langmu;

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Article highlights

- The epidemic of DM has become an emerging public health concern in recent years, and DR is the commonest cause of irreversible visual loss at a working age worldwide and PDR is the prevalent cause of blindness among these patients.
- Recently, many studies confirmed the effectiveness of preoperative intravitreal anti-VEGF therapy which is believed reduces many surgical procedures and complications, while possible side effects such as progression of vitreoretinal fibrosis should be kept in mind.
- This meta analysis showed that preoperative intravitreal VEGF inhibitors, reduce the surgical time, achieve fewer iatrogenic retinal breaks and subsequently reducing the need for SO tamponade, lessen intraoperative hemorrhage, and also lead fewer endodiathermy applications.
- This meta analysis showed improvement of clinical outcomes and reduction of complications in patients received adjuvant intravitreal Anti-VEGF 1-21 days before surgery. However, in order to prevent tractional complications, it is recommended to inject within 3 days before surgery.

Kanghong Inc., Sichuan, China), Aflibercept (Eylea, Regeneron), and Ranibizumab (Lucentis; Genentech Inc., CA) [6–8].

Preoperative intravitreal injection of anti-VEGF medications is a novel candidate for safer and more convenient vitrectomy in cases suffering from severe PDR, while possible side effects such as progression of vitreoretinal fibrosis should be kept in mind [9,10]. Although, the prevention of this complication may be achieved by timing of preoperative injection. However, the proper timing for injection with maximum benefits and minimum side effects is not clear. In this review, we evaluated the proper time point and effectiveness of preoperative intravitreal anti-VEGF therapy as an adjuvant in severe PDR candidates for PPV.

2. Methods

The current study was approved by the research ethics committees of school of medicine-Kermansha University of Medical Science (code: IR.KUMS.MED.REC.1401.156). This study was carried out according to the instructions for systematic review [11] in four steps, which is explained in detail as following (methodology illustrated in Figure 1):

2.1. Literature search

An encyclopedic study search was organized using MEDLINE and EMBASE till Apr 2022 with English language restriction. All manuscripts which reported efficacy of intravitreal anti-VEGF injection before PPV in PDR were collected with search strategy according to the medical subject heading (MeSH) terms as below:

((((vitrectomy) OR (pars-plana vitrectomy) OR (PPV))) AND ((diabetic retinopathy) OR (proliferative diabetic retinopathy) OR (PDR) OR (DR) OR (tractional retinal detachment) OR (TRD))) AND ((anti-VEGF) OR (vascular endothelial growth factor) OR (VEGF))

Then, a broad manual literature search was carried out in the following journals: American Journal of Ophthalmology (https://www.ajo.com), Progress in Retinal and Eye Research (https://www.journals.elsevier.com/progress-in-retinal-and-eye-research), Acta ophthalmologica (www.onlinelibrary.wiley.com/journal/17553768), Current Opinion in Ophthalmology

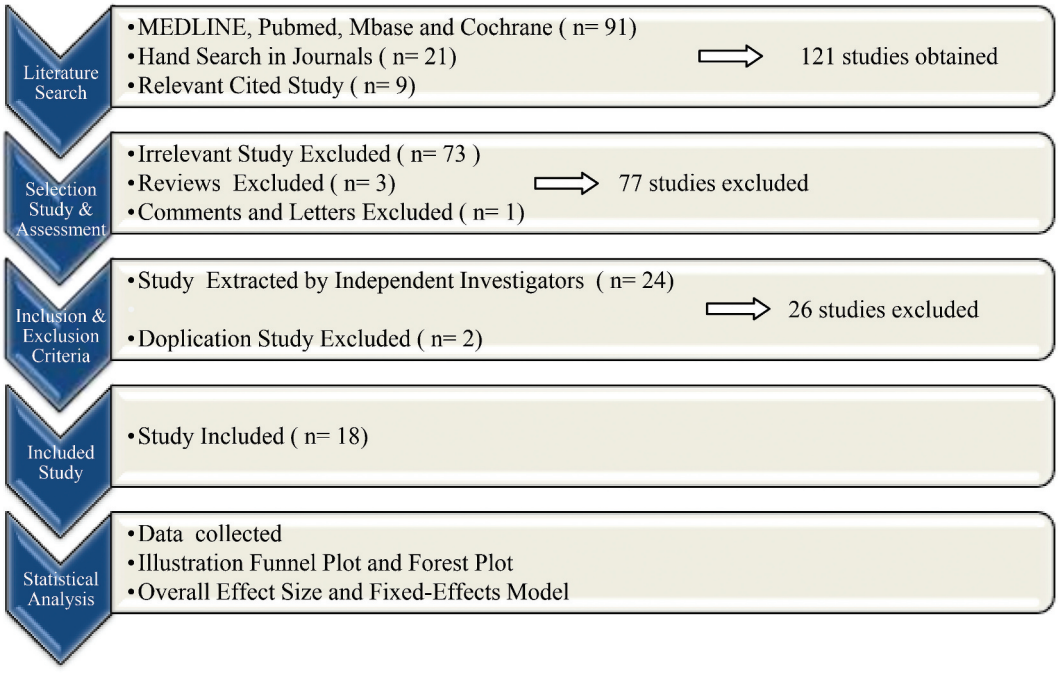

Figure 1. This figure show the methodology of the study step by step. During an encyclopedic literature search and survey of relevant cited studies, number of 121 studies was founded where 77 excluded in the second step (irrelevant studies, reviews, comments, and letters). After reviewing the inclusion and exclusion criteria, 26 more studies were excluded and finally, 18 studies were included for statistical analysis.

(https://journals.lww.com/co-ophthalmology/pages/default.aspx), Retina (https://journals.lww.com/retinajournal), and JAMA Ophthalmology (https://jamanetwork.com/journals/jamaophthalmology).

Then, references of the assessed manuscripts were surveyed to find relevant studies. A total of 3697 articles were found.

2.2. Selection Study & Assessment

After a brief review of abstracts, the articles that were most relevant to our topic were selected, and those which reported PPV in PDR with adjuvant preoperative anti-VEGF injection were thoroughly studied. A 103 articles were found in this step and full-text versions of all were obtained.

2.3. Inclusion & exclusion criteria

All clinical trials that have a control group and examined the five desired factors to evaluate the clinical effectiveness of anti-VEGF adjuvant injection (i.e. the incidence of intraoperative hemorrhage, iatrogenic retinal break, duration of surgery, the necessity for relaxing retinotomy, and silicone oil (SO) injection as endocular tamponade) were included in the study. To prevent potential bias or errors, the quality of the studies were assessed by three independent researchers considering the CHARMS [12] and then data extraction was done. Disagreements were resolved through consensus or discussion with a fourth reviewer if needed. Eventually, 18 papers on surgical outcome of PPV in PDR with preoperative adjuvant intravitreal anti-VEGF were included, which covered 1165 cases.

2.4. Statistical analysis

At first, public information, such as the first name of the authors, publication date, sample size, duration of study, demographic pattern of patients, and etc, was extracted (Table 1).

Comprehensive Meta-Analysis.2 (CMA.2) software was used for data analysis. Heterogeneity index was evaluated by the I2 test. In case of substantial heterogeneity ($I2 > 50\%$), a random-effects model was applied. Otherwise, for non-significant heterogeneity ($I2 \leq 50\%$), we used a fixed-effects model [53]. Level of significance for pooled effect and heterogeneity was set at $P < 0.05$. Because of non-significant I2, the fixed-effects model estimated the overall effect size. The publication bias was checked by the funnel plot (Figure 2).

3. Results

During the search process, 121 articles were found until 30 April 2022, and with the English language limit, 91 articles in MEDLINE, Pubmed, EMBASE, and Cochrane databases and 21 articles by manual search in journals and website referenced in the articles. Among these, 77 unrelated studies were excluded based on the title and abstract review and 44 studies were selected. The full text of all these articles was received and general information such as the manuscript title, the first author, place of implementation of the study, the publication date, the study design, the sample size along with the demographic information of the participants, and the duration of diabetes in them were extracted (Table 1). After the review of the researchers, 16 articles with an average consensus of 85% were included in the study, and in two cases of disagreement, the articles were reviewed by the fourth researcher and selected with his approval. Finally, 18 clinical trials with a total sample size of 1165 (623 in intervention group and 542 in control group) that investigated the efficacy of adjuvant intravitreal injection of Anti-VEGF on the results of PPV for TRD in diabetic patients compared to the control group were included. Due to the heterogeneity of studies' methodology, to check the appropriate timing of injection, patients were divided into three time groups: injection 72 hours before surgery, injection 3–7 days before surgery, and injection 7–21 days before surgery. Five studies had injections less than 3 days, 12 studies 3–7 days, and 2 studies 7–21 days before surgery, which, respectively, included 169, 418, and 36 patients in the intervention group.

Five factors were investigated to evaluate the clinical effectiveness of anti-VEGF adjuvant injection, including the incidence of intraoperative hemorrhage, iatrogenic retinal break, duration of surgery, the necessity for relaxing retinotomy, and SO injection as endocular tamponade. The included articles were classified based on the investigated factors and all data were extracted (Table 2).

3.1. Intraoperative hemorrhage

In all three groups, the rate of intraoperative bleeding was lower than the control group (without adjuvant injection of anti-VEGF). The lowest risk of bleeding was in the group injected 7–21 days before surgery (OR: 0.104, 0.039–0.275, p: 0.000), followed by the groups with injection 3–7 days (OR: 0.198, 0.131–0.300, p: 0.000) and 72 hours (OR: 0.227, 0.112–0.462, p: 0.000) before surgery, respectively (Figure 3).

3.2. Incidence rate of iatrogenic retinal break

In all three groups, the incidence of iatrogenic retinal break during surgery was lower than the control group (without adjuvant anti-VEGF injection). It should be noted that in the injection group 72 hours before surgery, the incidence of iatrogenic retinal break was lower than the other two groups (OR: 0.212, 0.087–0.516, p: 0.001) (Figure 4).

Table 1. During the search strategy process in databases and manual search in journals and website referenced in the articles 121 articles were found. After a brief review of abstracts, these 44 articles that were most relevant to our topic were selected and thoroughly studied. (T/C: Therapeutic group/Comparison group, SD: Standard deviation, DM: Diabetes mellitus, N/A: Not available, RCT: Randomized clinical trial, CT: Clinical trial).

Study	First author	City (University)	Publication date	Study design	Sample (T/C)	Mean age±SD (Years)	Male/Female	Duration of DM ± SD (Years)
The efficacy and safety of intravitreal injection of Ranibizumab as pre-treatment for vitrectomy in proliferative diabetic retinopathy with vitreous hemorrhage [13]	Shengguo Li	The Second Xiangya Hospital, Central South University, Changsha, China	2022 (2016–2018)	Pilot RCT	48 (32/16)2 intervention group (T1:16, T2:16) 2 intervention group (T1:16, T2:16)	T1: 46.9 ± 11.7 T2: 49.8 ± 10.1 C: 53.1 ± 6.3	T1: 9/7 T2: 10/6 C: 8/8	N/A
Pars plana vitrectomy assisted by intravitreal injection of conbercept enhances the therapeutic effect and quality of life in patients with severe proliferative diabetic retinopathy [14]	Qin Wang	Chongqing Aier Eye Hospital, Chongqing, Chongqing, China	2022 (2019–2021)	Retrospective study	48 (26/22)	T: 55.08 ± 9.72 C: 55.95 ± 11.11	T: 16/10 C: 13/9	T: 5.15 ± 1.76 C: 5.95 ± 1.84
Potential bias of preoperative intravitreal anti-VEGF injection for complications of proliferative diabetic retinopathy [15]	Kei Takayama	National Defense Medical College, Tokorozawa, Japan	2021 (2010–2016)	Retrospective study	409 (87/322)	T: 50.6 ± 11.9 C: 58.9 ± 12.5	T: 55/32 C: 210/112	T: 10.1 ± 9.1 C: 12.6 ± 10.3
Vascular endothelial growth factor concentration in vitreous humor of patients with severe proliferative diabetic retinopathy after intravitreal injection of conbercept as an adjunctive therapy for vitrectomy [16]	Bing Li	Peking Union Medical College Hospital, Peking Union Medical College, Beijing, China	2020(2016–2018) (2016–2018)	RCT	80 (40/40)2 intervention & control groups (T1: 20, T2: 20, C1: 20, C2: 20) 2 intervention & control groups (T1: 20, T2: 20, C1: 20, C2: 20)	T1: 51.1 ± 11.6 T2: 53.1 ± 10.0 C1: 56.0 ± 10.5 C2: 54.3 ± 14.3	T1: 13/7 T2: 10/10 C1: 9/11 C2: 9/11	T1: 10.9 ± 7.7 T2: 11.8 ± 6.9 C1: 14.0 ± 6.8 C2: No DM
Ranibizumab Pretreatment in Vitrectomy with Internal Limiting Membrane Peeling on Diabetic Macular Edema in Severe Proliferative Diabetic Retinopathy [3]	Jian Guan	Hospital of China Medical University, Shenyang, Liaoning Province, China	2020(2013–2015) (2013–2015)	Non-randomized CT	63 (31/32)	T: 58.87 ± 3.02 C: 59.47 ± 3.56	T: 15/6 C: 15/17	T: 16.48 ± 2.19 C: 16.16 ± 2.4
Effect of intravitreal ranibizumab pretreatment on vitrectomy in young patients with proliferative diabetic retinopathy [2]	Hui-Jin Chen	Peking University Third Hospital, Beijing, China	2020(2016–2017) (2016–2017)	Non-randomized CT	50 (25/25)	T: 34.2 ± 6.7 C: 35.5 ± 5.8	T: 14/11 C: 12/13	T: 9.3 ± 5.2 C: 10.0 ± 5.9
Intravitreal conbercept injection as an adjuvant in vitrectomy with silicone oil infusion for severe proliferative diabetic retinopathy [17]	Shuang Gao	Ruijin Hospital Affiliated Shanghai Jiaotong University School of Medicine, Shanghai, China	2020 (2016–2017)	RCT	983 intervention groups (T1: 34, T2: 35, T3: 29) 3 intervention groups (T1: 34, T2: 35, T3: 29)	T1: 50.76 ± 13.47 T2: 53.97 ± 14.76 T3: 52.55 ± 14.62	T1: 14/20 T2: 16/19 T3: 16/13	T1: 14.5 ± 5.1 T2: 12.8 ± 5.2 T3: 12.6 ± 5.2
Preoperative Intravitreal Conbercept Facilitates Vitrectomy in Proliferative Diabetic Retinopathy: Is Attention Required for the Fellow Eye? [9]	Wei Xu	The First Affiliated Hospital of Fujian Medical University, Fuzhou, China	2019(2015–2018) (2015–2018)	Retrospective study	37 (16/21)	T: 50.1 ± 10.1 C: 51.9 ± 8.3	T: 7/9 C: 10/11	T: 8.8 ± 5.0 C: 7.0 ± 4.0
Ziv-aflibercept versus bevacizumab administration prior to diabetic vitrectomy: A randomized and controlled trial [18]	Isaac Aleman	Hospital La Carlota, Montemorelos, Nuevo León, México	2019 (2016–2018)	RCT	1732 intervention groups (T1:82, T2: 91) 2 intervention groups (T1:82, T2: 91)	T1: 58 ± 2.1 T2: 55.8 ± 2.0	T1:44/38 T2: 47/44	N/A
Preoperative Bevacizumab for Tractional Retinal Detachment in Proliferative Diabetic Retinopathy: A Prospective Randomized Clinical Trial [19]	J.Fernando Arevalo	Johns Hopkins University, Baltimore, Maryland, USA	2019 (2013–2015)	RCT	214 (102/112)	T: 59.5 ± 11 C: 61.3 ± 10	T: 63/39 C: 60/52	N/A

(*Continued*)

Table 1. (Continued).

Study	First author	City (University)	Publication date	Study design	Sample (T/C)	Mean age±SD (Years)	Male/Female	Duration of DM ± SD (Years)
Conbercept and ranibizumab pretreatments in vitrectomy with silicone oil infusion for severe diabetic retinopathy [7]	Kai-Bo Yang	The First Hospital of China Medical University, Shenyang, China	2019(2015–2016) (2015–2016)	Retrospective chart review study	792 intervention group (T1: 37, T2: 42) 2 intervention group (T1: 37, T2: 42)	T1: 49.7 ± 12.2 T2: 51.5 ± 13.3	T1: 19/16 T2: 21/18	N/A
Efficacy comparison of intravitreal injections of conbercept and ranibizumab for severe proliferative diabetic retinopathy [20]	Qianyi Lu	First Affiliated Hospital of Soochow University, Suzhou, China	2018(2014–2015) (2014–2015)	Retrospective, Cross-sectional study	428(303/125)2 intervention groups (T1: 146, T2: 157) 2 intervention groups (T1: 146, T2: 157)	T1: 53.33 ± 7.27 T2: 51.44 ± 8.33 C: 52.13 ± 6.71	T1: 78/68 T2: 84/73 C: 67/58	N/A
Efficacy and Safety of Intravitreal Conbercept, Ranibizumab, and Triamcinolone on 23-Gauge Vitrectomy for Patients with Proliferative Diabetic Retinopathy [21]	Jinglin Cui	The First Hospital of Qiqihar City, Qiqihar, Heilongjiang, China	2018(Jan-Dec 2015) (Jan- Dec 2015)	RCT	603 intervention group (T1: 20, T2: 19, T3: 19) 3 intervention group (T1: 20, T2: 19, T3: 19)	T1: 60.74 ± 2.63 T2: 55.28 ± 5.16 T3: 57.49 ± 4.22	T1: 11/9 T2: 13/6 T3: 11/8	T1: 24.25 ± 6.33 T2: 28.76 ± 5.27 T3: 25.98 ± 4.6
Effect of intravitreal conbercept treatment before vitrectomy in proliferative diabetic retinopathy [22]	Jian-Bo Mao	Affiliated Eye Hospital of Wenzhou Medical University, Hangzhou, Zhejiang Province, China	2018(2014–2016) (2014–2016)	Retrospective chart review study	68 (22/46)	T: 52.73 ± 9.20 C: 57.52 ± 9.47	T: 13/9 C: 21/25	T: 9.27 ± 6.50 C: 13.54 ± 9.47
Bevacizumab before diabetic vitrectomy: A clinical trial assessing 3 dosing amounts [23]	Javier Castillo Velazquez	Hospital La Carlota, Nuevo Leon, Mexico	2018 (2015–2017)	RCT	1673 intervention groups (T1: 65, T2: 43, T3:59) 3 intervention groups (T1: 65, T2: 43, T3:59)	T1: 57.3 ± 2.3 T2: 55.6 ± 2.9 T3: 56.3 ± 2.5	T1: 30/35 T2: 15/28 T3: 29/30	N/A
Concentrations of VEGF and PlGF decrease in eyes after intravitreal conbercept injection [24]	Jun Zhou	Hospital, Xi'an Jiaotong University Health Science Center, Hanzhong, Shaanxi, China	2018	RCT	25 (8/17)2 control groups (C1: 8, C2: 9) 2 control groups (C1: 8, C2: 9)	T: 50.1 ± 13.0 C1: 55.4 ± 9.7 C2: 50.1 ± 6.1	T: 5/3 C1: 2/6 C2: 7/2	N/A
Preoperative Bevacizumab Administration in Proliferative Diabetic Retinopathy Patients Undergoing Vitrectomy: a Randomized and Controlled Trial Comparing Interval Variation [25]	Javier Castillo Velazquez	Hospital La Carlota, Nuevo Leon, Mexico	2017 (2015–2016)	RCT	1252 intervention groups (T1: 67, T2: 58) 2 intervention groups (T1: 67, T2: 58)	T1: 54.9 ± 2.2 T2: 57.4 ± 2.4	T1: 32/35 T2: 27/31	N/A
Ranibizumab pretreatment in diabetic vitrectomy: A pilot randomized controlled trial (the radivit study) [26]	O Comyn	Moorfields Eye Hospital and University College London (UCL), London, UK	2017	RCT	30 (15/15)	T: 57.1 ± 14 C: 48.7 ± 18	T: 3/12 C: 9/6	T: 19 C: 21
Intravitreal conbercept (KH902) for surgical treatment of severe proliferative diabetic retinopathy [27]	Long Su	Tianjin Medical University Eye Institute, Tianjin, China	2016	RCT	36 (18/18)	N/A	N/A	N/A

(*Continued*)

Table 1. (Continued).

Study	First author	City (University)	Publication date	Study design	Sample (T/C)	Mean age±SD (Years)	Male/Female	Duration of DM ± SD (Years)
A Randomized Controlled Trial of Conbercept Pretreatment before Vitrectomy in Proliferative Diabetic Retinopathy [28]	Xiaochun Yang	The Affiliated Hospital of Kunming University of Science and Technology, Yunnan, China	2016(2014–2015) (2014–2015)	RCT	107 (54/53)	T: 48.63 ± 8.24 C: 49.64 ± 8.71	T: 27/16 C: 24/21	T: 16.67 ± 4.53 C: 15.87 ± 4.77
Randomized controlled study of intravitreal bevacizumab 0.16 mg injected one day before surgery for proliferative diabetic retinopathy [29]	Ayumu Manabe	Nihon University, Chiyodaku, Japan	2015(2012–2013) (2012–2013)	RCT	66 (34/32)	T: 59.9 ± 11.8 C: 59.2 ± 12.9	T: 22/10 C: 32/2	N/A
Changes in vitreous VEGF, bFGF and fibrosis in proliferative diabetic retinopathy after intravitreal bevacizumab [30]	Jiu-Ke Li	Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, Zhejiang, China	2015 (2012–2013)	RCT	68 (53/15)3 intervention group (T1: 23, T2: 11, C1: 19, C2: 15) 3 intervention group (T1: 23, T2: 11, C1: 19, C2: 15)	T1 & T2: 48.9 ± 11.2 C1: 53.9 ± 8.5 C2: 58.7 ± 6.6	T1 & T2: 19/15 C1: 10/9 C2: 6/9	T1 & T2: 7.24 ± 3.51 C1: 7.40 ± 4.95
A randomized study comparing the efficacy of bevacizumab and ranibizumab as pre-treatment for pars plana vitrectomy in proliferative diabetic retinopathy [31]	Kaivon Pakzad-Vaezi	University of British Columbia, Vancouver, British Columbia, Canada	2014	RCT	292 intervention group (T1: 14, T2: 15) 2 intervention group (T1: 14, T2: 15)	T1: 52.8 ± 10.5 T2: 51.6 ± 12.3	T1: 11/3 T2: 6/9	N/A
The effect of intravitreal bevacizumab as a pretreatment of vitrectomy for diabetic vitreous hemorrhage on recurrent hemorrhage [32]	Sule Berk Ergun	Ankara Ataturk Training and Research Hospital, Ankara, Turkey	2013(2008–2011) (2008–2011)	Retrospective chart review study	65 (19/46)	T: 59.74 ± 9.30 C: 59.79 ± 8.30	T: 12/7 C: 30/16	N/A
Intravitreal Avastin as an adjunct in patients with proliferative diabetic retinopathy undergoing pars plana vitrectomy [33]	Yawar Zaman	Al-Ibrahim Eye Hospital, Isra Post Graduate Institute of Ophthalmology, Karachi, Pakistan.	2013(2010–2011) (2010–2011)	RCT	54 (30/24)	52.07 ± 5.54 (Overall)	32/22 (Overall)	N/A
Effect of bevacizumab injection before vitrectomy on intravitreal hemorrhage in pseudophakic patients with proliferative diabetic retinopathy [34]	Mehmet Demir	Sisli Etfal Training and Research Hospital, Department of Ophthalmology, Istanbul, Turkey.	2013 (2008–2012)	Retrospective study	44 (22/22)	T: 60.7 ± 7.80 C: 58.8 ± 9.03	T: 10/12 C: 8/14	N/A
Early vitreous hemorrhage after vitrectomy with preoperative intravitreal bevacizumab for proliferative diabetic retinopathy [35]	Tatsuhiko Sato	Osaka Rosai Hospital, Clinical Research Center for Occupational Sensory Organ Disability, Kita-Ku, Sakai, Japan	2013(2006–2008) (2006–2008)	RCT	71 (25/46)	T: 48.9 ± 14.1 C: 57.5 ± 10.5	T: 5/12 C: 13/24	N/A
Six-month visual outcome after pars plana vitrectomy in proliferative diabetic retinopathy with or without a single preoperative injection of intravitreal bevacizumab [36]	Amod Gupta	Dogra Advanced Eye Centre, Post Graduate Institute of Medical Education and Research, Chandigarh 160,012, India	2012(2005–2008) (2005–2008)	Retrospective chart analysis	181 (94/87)	T: 51.57 ± 9.88 C: 52.6 ± 8.55	T: 49/34 C: 51/28	T: 11.18 ± 6.68 C: 10.89 ± 5.82

(*Continued*)

Table 1. (Continued).

Study	First author	City (University)	Publication date	Study design	Sample (T/C)	Mean age±SD (Years)	Male/Female	Duration of DM ± SD (Years)
Bevacizumab prior to vitrectomy for diabetic traction retinal detachment [37]	R. Pokroy	Department of Ophthalmology and Eye Care Services, Henry Ford Hospital, Detroit, MI, U.S.A..	2012(2004–2009) (2004–2009)	Retrospective chart review study	99 (34/65)	T: 46.72 ± 5.85 C: 51.61 ± 6.35	T: 21/13 C: 34/31	T: 16.37 ± 8.7 C: 18.05 ± 8.05
Intravitreal bevacizumab increases intraocular interleukin-6 levels at 1 day after injection in patients with proliferative diabetic retinopathy [38]	Sohee Jeon	Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea	2012 (Jul-Oct 2011)	RCT	302 intervention group (T1: 15, T2: 15) 2 intervention group (T1: 15, T2: 15)	T1: 58.7 ± 9.7 T2: 55.8 ± 10.6	T1: 10/5 T2: 9/6	T1: 15.4 ± 7.5 T2: 14.3 ± 5.8
Effects of bevacizumab on the neovascular membrane of proliferative diabetic retinopathy: Reduction of endothelial cells and expressions of vegf and hif-1α [39]	Xiao-Xia Han	Xijing Hospital, Fourth Military Medical University, Shaanxi, China	2012 (2008–2009)	RCT	24 (12/12)	T: 50.3 ± 7.6 C: 53.2 ± 5.1	T: 6/6 C: 7/5	T: 11.9 ± 6.0 C: 17.1 ± 3.8
The effect of adjunctive intravitreal bevacizumab for preventing postvitrectomy hemorrhage in proliferative diabetic retinopathy [40]	Jeeyun Ahn	Seoul National University College of Medicine, Seoul, Korea. Seoul National University Bundang Hospital, Seongnam, Korea.	2011	RCT	107 (73/34)2 intervention group (T1: 36, T2: 37) 2 intervention group (T1: 36, T2: 37)	T1: 51.0 ± 9.5 T2: 55.6 ± 10.3 C: 55.0 ± 11.4	T1: 23/13 T2: 21/16 C: 16/18	–
Preoperative injection of intravitreal bevacizumab in dense diabetic vitreous hemorrhage [41]	Mohammad Sadegh Farahvash	Farabi Eye Hospital, Department of Ophthalmology, Tehran University of Medical Sciences, Tehran, Iran.	2011(2008–2009) (2008–2009)	RCT	35 (18/17)	T: 58.3 (49–73) C: 58.7 (37–72)	T: 7/11 C:11/6	T: 13.5 (2–30) C: 10.1 (1–30)
Intravitreal bevacizumab for surgical treatment of severe proliferative diabetic retinopathy [42]	Raffaello di Lauro	Department of Ophthalmology, University of Molise, Campobasso, Italy	2010(2005–2007) (2005–2007)	RCT	72 (68/34)2 intervention group (T1: 34, T2: 34) 2 intervention group (T1: 34, T2: 34)	N/A	N/A	N/A
Experience with intravitreal bevacizumab as a preoperative adjunct in 23-G vitrectomy for advanced proliferative diabetic retinopathy [43]	Sergio E. Hernandez-Da Mota	General Hospital Dr. Miguel Silva, and Retina Department, Clnica David-Unidad Oftalmologica, Morelia, Michoacan – Mexico	2010	RCT	40 (20/20)	T: 55.7 ± 9.9 C: 55.7 ± 7.4	T: 14/6 C: 10/10	N/A
Effect of intravitreal bevacizumab injection before vitrectomy on proliferative diabetic retinopathy [44]	Cai-Rui Li	Hospital of Dali University, Dali, Yunnan Province, China	2010(2006–2009) (2006–2009)	Retrospective study	46 (18/28)	T: 42 ± 9 C: 43 ± 12	T: 10/8 C: 12/16	N/A
Dose of intravitreal bevacizumab (avastin) used as preoperative adjunct therapy for proliferative diabetic retinopathy [45]	Takayuki Hattori	Nihon University, Kanda, Chiyodaku, Tokyo, Japan.	2010 (2006–2008)	Non-Randomized CT	52 (12/40)	T: 55.8 ± 12.0 C: 60.1 ± 8.5	N/A	N/A
Intravitreal injection of bevacizumab before vitrectomy for proliferative diabetic retinopathy [46]	Mehdi Modarres	Iran University of Medical Sciences, Tehran, Iran	2009	RCT	40 (22/18)	T: 55.8 ± 11.3 C: 53.2 ± 11.7	N/A	N/A

(*Continued*)

Table 1. (Continued).

Study	First author	City (University)	Publication date	Study design	Sample (T/C)	Mean age±SD (Years)	Male/Female	Duration of DM ± SD (Years)
Bevacizumab pretreatment in vitrectomy with silicone oil for severe diabetic retinopathy [47]	Po-Ting Yeh	National Taiwan University Hospital, Taipei, Taiwan	2009(2006–2007) (2006–2007)	RCT	41 (20/21)	T: 49.4 ± 7.9 C: 51.0 ± 7.7	T: 11/9 C:/13	T: 5 patients < 10y, 15 ≥ 10y C: 9 patients < 10y, 12 ≥ 10y
Intraoperative bleeding during vitrectomy for diabetic tractional retinal detachment with versus without preoperative intravitreal bevacizumab (ibetra study) [48]	D da R Lucena	School of Medicine of Ribeirao Preto, Sao Paulo, Brazil	2009 (Mar-May 2008)	RCT	20 (10/10)	T: 54.4 C: 55.6	T: 6/4 C: 4/6	T: 13.8 C: 16.3
Intravitreal bevacizumab for prevention of early postvitrectomy hemorrhage in diabetic patients: A randomized clinical trial [49]	Hamid Ahmadieh	Shahid Beheshti University of Medical Sciences, Tehran, Iran	2009 (Jan-Dec 2007)	RCT	68 (35/33)	T: 53.6 ± 11.7 C: 56.7 ± 10.4	T: 17/18 C: 17/16	N/A
Intravitreal bevacizumab as an adjunctive therapy before diabetic vitrectomy [50]	Ashraf M El-Batarny	Chief of Vitreoretinal Service, Magrabi Eye and Ear Hospital, Muscat, Sultanate of Oman	2008	RCT	30 (15/15)	T: 44 ± 11 C: 46 ± 12	N/A	N/A
Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR) [51]	Stanislao Rizzo	Eye Surgery Clinic, Santa Chiara Hospital, Pisa, Italy	2008	RCT	22 (11/11)	N/A	N/A	N/A
Bevacizumab pretreatment and long-acting gas infusion on vitreous clear-up after diabetic vitrectomy [52]	Chung-May Yang	National Taiwan University and the Department of Ophthalmology, En Chu Kong Hospital, Taipei, Taiwan.	2008(2006–2007) (2006–2007)	Nonrandomized CT	40 (16/24)	T: 44.4 ± 11.4 C: 50.2 ± 10.9	T: 8/8 C: 10/14	T: 6 patients < 10y, 10 ≥ 10y C: 10 patients < 10y, 14 ≥ 10y

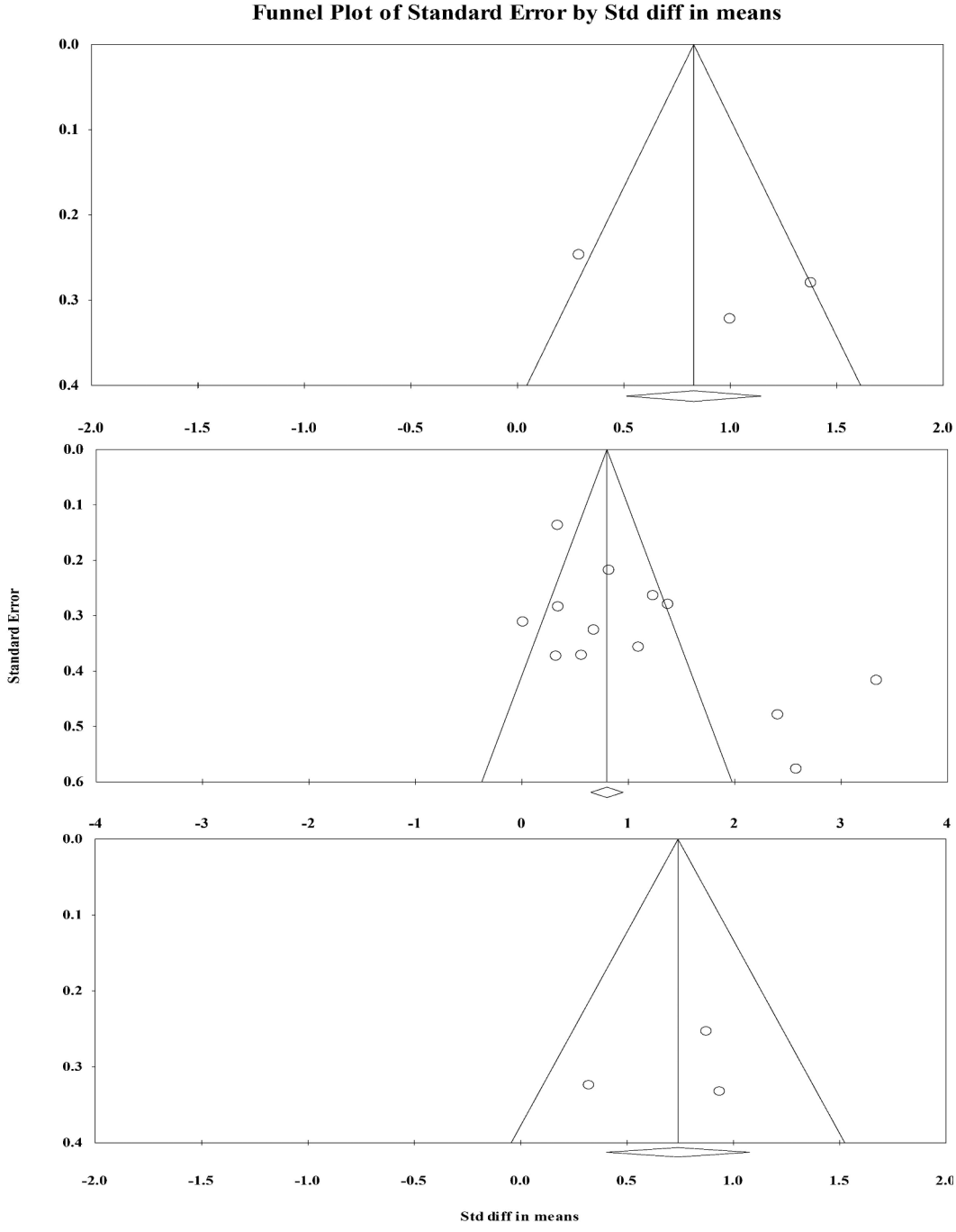

Figure 2. Funnel plot for sample size and effect size of studies investigating surgical time as one of the criteria for the efficacy of adjuvant intravitreal injection of anti-VEGF on the results of PPV for TRD in diabetic patients in 3 studies groups, injection.

3.3. Duration of surgery

In all three groups, the duration of surgery was significantly less than the control group (without adjuvant injection of Anti-VEGF). However, the surgery time was minimal in the injection group 7–21 days before surgery (Std diff: 0.740, SE: 0.172, p: 0.000) and then the groups with 3–7 days (Std diff: 0.800, SE: 0.077, p: 0.000) and 72 hours injection before surgery (Std diff: 0.828, SE: 0.161, p: 0.000), respectively. But the surgery time is not significantly different in these three groups (Figure 5).

Table 2. Eighteen clinical trials that investigated the efficacy of adjuvant intravitreal injection of anti-VEGF on the results of PPV for TRD in diabetic patients compared to the control group were included in this review. Due to the heterogeneity of studies' methodology, to check the appropriate timing of injection, patients were divided into three time groups: G1 (injection 72 hours before surgery), G2 (injection 3–7 days before surgery), and G3 (injection 7–21 days before surgery). (anti-VEGF: Anti vascular endothelial growth factor, min: Minutes, SO: Silicone oil, Pre-OP: Preoperative, Post-OP: Postoperative, BCVA: Best corrected visual acuity, mg: Milligram,ml: Milliliter, T/C: Therapeutic group/Comparison group, N/A: Not available, PPV: pars plana vitrectomy, TRD: tractional retinal detachment).

Study	Anti-VEGF agent (dosage)	Timing for Anti-VEGF injection (days before surgery)	Intra operative bleeding rate	Hemostatic techniques (Endodiathermy)	Surgical time (min)	Iatrogenic break	Relaxing Retinotomy	Endoocular tamponade (S.O/Gas)	Pre-OP BCVA	Post-OP BCVA (Months)
Shengguo Li, et al (2022) [13]	T1, T2: Ranibizumab (0.5 mg/0.05 ml) C: Sham subconjunctival injection	T1: 1 (G1) T2: 3 (G1) C: 3	T1: 2/16T: 1/16C: 12/16 T: 1/16 C: 12/16	T1: 1/16 T2: 1/16 C: 9/16	T1: 96.5 ± 16.7 T2: 86.2 ± 18.8 C: 110.6 ± 21.9	T1: 1/16 T2: 0/16 C: 5/16	T1: 0/16 T2: 0/16 C: 1/16	T1: 2 SO/3 GasT2: 2 SO/4 GasC: 9 SO/2 Gas T2: 2 SO/4 Gas C: 9 SO/2 Gas	T1: 1.98 ± 0.46T2: 2.05 ± 0.41C: 2.00 ± .42 T2: 2.05 ± 0.41 C: 2.00 ± 0.42	T1: .48 ± 0.18T2: .46 ± 0.15C: .70 ± .27 T2: 0.46 ± 0.15 C: 0.70 ± 0.27
Bing Li, et al (2020) [16]	Conbercept (0.5 mg/0.05 m)	T1: 7 (G2) T2: 14 (G3)	T1: 6/20T2: 6/20C1: 15/20C2: – T2: 6/20 C1: 15/20 C2: –	T1: 0/6 T2: 0/6 C1: 14/15 C2: –	T1: 54.0 ± 12.6 T2: 59.0 ± 17.8 C1: 78.9 ± 24.1 C2: –	N/A	N/A	N/A	N/A	N/A
Jian Guan, et al (2020) [3]	Ranibizumab (0.5 mg/0.05 ml)	T: 3 (G1)	T: 4/31C: 12/32 C: 12/32	T: 2/4 C: 12/12	T: 92.60 ± 9.65 C: 135.41 ± 42.39	T: 3/31 C: 21/32	N/A	T: 4 SOC: 13 SO C: 13 SO	T: 1.56 ± 0.62C: 1.52 ± .52 C: 1.52 ± 0.52	T: .38 ± 0.13C: .41 ± .10(6 M) C: 0.41 ± 0.10 (6 M)
Hui-Jin Chen, et al (2020) [2]	Ranibizumab (0.5 mg/0.05 mL)	T: 3–5 (G2)	T: 7/25C: 14/25 C: 14/25	T: 3/7 C: 7/14 (>5 spots endodiathermy)	T: 73.2 ± 32.8 C: 85.6 ± 37.9	T: 8/25 C: 9/25	T: 1/25 C: 1/25	T: 6 SOC: 7 SO C: 7 SO	T: 2.05 ± 0.9C: 2.25 ± .8 C: 2.25 ± 0.8	T: .47 ± 0.29C: .58 ± .32(12 M) C: 0.58 ± 0.32 (12 M)
Shuang Gao, et al (2020) [17]	Conbercept (0.5 mg/0.05 ml)	T1: 3–5 before PPV (G2) T2: 3–5 before PPV + at the end of surgery (G2) C: At the end of surgery	T1: 7/34T2: 6/29C: 12/35(severe intraoperative bleeding) T2: 6/29 C: 12/35 (severe intraoperative bleeding)	T1: 1.73 ± 1.26 T2: 1.34 ± 0.81 C: 3.00 ± 1.14	T1: 55.4 ± 11.2 T2: 57.8 ± 13.2 C: 67.6 ± 15.1	N/A	N/A	N/A	T1: 1.95 ± 0.43T2: 1.98 ± 0.44C: 1.97 ± .37 T2: 1.98 ± 0.44C: 1.97 ± 0.37	T1: 1.25 ± 0.45T2: 1.16 ± 0.44C: 1.29 ± .46(6 M) T2: 1.16 ± 0.44 C: 1.29 ± 0.46 (6 M)
J.Fernando Arevalo, et al (2019) [19]	Bevacizumab (1.25 mg, 0.05 mL)	3–5 (G2)	T: 69/102C: 100/112 C: 100/112	T: 28/102 C: 75/112	T: 71.3 ± 32.1 C: 83.6 ± 38.7	T: 35/102 C: 66/112	N/A	T: 24 SOC: 48 SO C: 48 SO	T: 1.1 ± 0.5C: 1.1 ± 1.4 C: 1.1 ± 1.4	T: .6 ± 0.48C: .7 ± .31(12 M) C: 0.7 ± 0.31 (12 M)
Jinglin Cui, et al (2018) [21]	T1: Conbercept (0.5 mg/0.05 ml) T2: Ranibizumab (0.5 mg/0.05 ml) C: Triamcinolone Acetonide (4 mg (0.5 ml, 8 mg/ml))	T1: 3–7 (G2) T2: 3–7 (G2) C: During surgery	T1:2/20T2: 3/19C: 9/19 T2: 3/19 C: 9/19	T1: 5 T: 6 C: 12	T1: 56.65 ± 6.52 T2: 54.89 ± 6.46 C: 77.32 ± 6.36	T1: 2/20 T2: 2/19 C: 8/19	N/A	T1: 9 SOT2: 9 SOC: 15 SO T2: 9 SO C: 15 SO	T1: 1.1 ± 0.2T2: 1.2 ± 0.2C: 1.11 ± .4 T2: 1.2 ± 0.2 C: 1.11 ± 0.4	T1: .65 ± 0.3T2: .7 ± 0.3C: .8 ± .2(6 M) T2: 0.7 ± 0.3 C: 0.8 ± 0.2 (6 M)
O Comyn, et al (2017) [26]	T: Ranibizumab (0.5 mg/0.05 ml) C: Sham injection	7 (G2)	T: 2C: 2(Intraoperative bleeding score) C: 2 (Intraoperative bleeding score)	T: 1.1 C: 1.5 (Mean Endodiathermy Spots)	T: 63 C: 51	N/A	T: 12/15 C: 15/15	T: 2 SO, 1 C3F8, 9 SF6C: 0 SO, 1 C3F8, 11 SF6 C: 0 SO, 1 C3F8, 11 SF6	T: 1.13C: 1.08 C: 1.08	T: 1.22C: 1.42 (12W) C: 1.42 (12W)
Long Su, et al (2016) [27]	Conbercept (10 mg/mL, 0.5 mg)	7 (G2)	T: 2/18C: 14/18 C: 14/18	T: 1/2 C: 8/14	T: 43 ± 8 C: 53 ± 10	T: 0/18 C: 3/18	T: 0/18 C: 1/18	T: 2 SOC: 12 SO C: 12 SO	T: 2.16 ± 0.86C: 1.75 ± .89 C: 1.75 ± 0.89	T: .97 ± 0.64C: 1.28 ± .97(6W) C: 1.28 ± 0.97 (6W)
Xiaochun Yang, et al (2016) [28]	Conbercept (0.05 mg/0.05 ml)	3 (G1)	T: 40/54C: 46/53 C: 46/53	T: 3/40 C: 10/46	N/A	N/A	N/A	N/A	N/A	N/A

(*Continued*)

Table 2. (Continued).

Study	Anti-VEGF agent (dosage)	Timing for Anti-VEGF injection (days before surgery)	Intra operative bleeding rate	Hemostatic techniques (Endodiathermy)	Surgical time (min)	Iatrogenic break	Relaxing Retinotomy	Endoocular tamponade (S.O/ Gas)	Pre-OP BCVA	Post-OP BCVA (Months)
Ayumu Manabe, et al (2015) [29]	Bevacizumab (0.16 mg/ 0.05 mL)	1 (G1)	N/A	T: 0.63 ± 1.0 C: 1.3 ± 1.4 (Mean Endodiathermy Spots)	T: 49 ± 20 C: 56 ± 27	T: 5/32 C: 5/34	N/A	T: 4 SO, 23 GasC: 6 SO, 24 Gas C: 6 SO, 24 Gas	T: 1.09 ± 0.6C: 1.14 ± .58 C: 1.14 ± 0.58	T: .46 ± 0.54C: .43 ± .48(1 M) C: 0.43 ± 0.48 (1 M)
Raffaello di Lauro, et al (2010) [42]	Bevacizumab (1.25 mg/0.05 ml)	T1: 7 (G2) T2: 21 (G2)	T1: 2/34T2: 3/34C: 19/ 34 T2: 3/34 C: 19/34	T1: 2/2 T2: 3/3 C: 13/19	T1: 65 ± 18 T2: 69 ± 21 C: 84 ± 12	T1: 0/34 T2: 1/34 C: 4/34	T1: 0/34 T2: 0/34 C: 1/34	T1: 2 SOT2: 3 SOC: 19 SO T2: 3 SO C: 19 SO	T1: 1.6 ± 0.8T2: 1.4 ± 1.0C: 1.6 ± 1.2 T2: 1.4 ± 1.0 C: 1.6 ± 1.2	T1: .78 ± 1.0T2: .9 ± 1.2C: 1.2 ± 1.4 (6 M) T2: 0.9 ± 1.2 C: 1.2 ± 1.4 (6 M)
Sergio E. HernÙndez-Da Mota, et al (2010) [43]	Bevacizumab (1.25 mg/0.05 ml)	2 (G1)	T: 20/20C: 20/20 C: 20/20	T: 1/20 C: 19/20	T: 8.05 C: 16.8 (effective time of vitrectomy)	N/A	T: 2/20 C: 7/20	N/A	T: 1.6C: 1.9 C: 1.9	T: 0.84C: 2.07(3 M) C: 2.07 (3 M)
Mehdi Modarres, et al (2009) [46]	Bevacizumab (2.5 mg/ 0.1 ml)	3–5 (G2)	T: 22/22C: 18/18 C: 18/18	T: 6.0 ± 4.3 C: 11.0 ± 5.8 (mean number of endodiathermy)	T: 62 ± 57.3 C: 95.5 ± 36	N/A	N/A	T: 10 SOC: 7 SO C: 7 SO	T: 1.9 ± 0.2C: 1.8 ± .2 C: 1.8 ± 0.2	T: 1.1 ± 0.53C: 1.2 ± .46(3 M) C: 1.2 ± 0.46 (3 M)
Po-Ting Yeh, et al (2009) [47]	Bevacizumab (1.25 mg/0.05 ml)	7 (G2)	T: 20/20C: 21/21 C: 21/21	T: 2/20 C: 16/21	T: 175.3 ± 41.5 C: 176.0 ± 32.5	T: 3/20 C: 6/21	N/A	N/A	N/A	N/A
Ashraf M El-Batarny, et al (2008) [50]	Bevacizumab (1.25 mg/0.05 ml)	5–7 (G2)	T: 4/15C: 15/15 C: 15/15	T: 4/4 C: 15/15 (mean number of endodiathermy)	T: 61.6 ± 14.5 C: 93.3 ± 11.6	N/A	T: 2/15 C: 4/15	T: 3 SO/9 SF6/3 Air) C: 9 SO/6 SF6) C: 9 SO/6 SF6)	T: 2.0 ± 0.86C: 1.79 ± .79 C: 1.79 ± 0.79	T: .74 ± 0.83C: .92 ± .82 C: 0.92 ± 0.82
Stanislao Rizzo, et al (2008) [51]	Bevacizumab (1.25 mg/0.05 ml)	5–7 (G2)	T: 5/11C: 11/11 C: 11/11	T: 2/11 C: 9/11	T: 57 ± 9 C: 83 ± 11	T: 0/11 C: 4/11	N/A	(SF6, C2F6) for all patients	T: 1.87C: 2.04 C: 2.04	T: 0.88C: 2.01(6 M) C: 2.01 (6 M)
Chung-May Yang, et al (2008) [52]	Bevacizumab (1.25 mg/0.05 ml)	7–9 (G3)	T: 16/16C: 24/24 C: 24/24	T: 2/16 C: 13/24	T: 120.2 ± 22.8 C: 110.6 ± 33.2	N/A	N/A	N/A	N/A	N/A

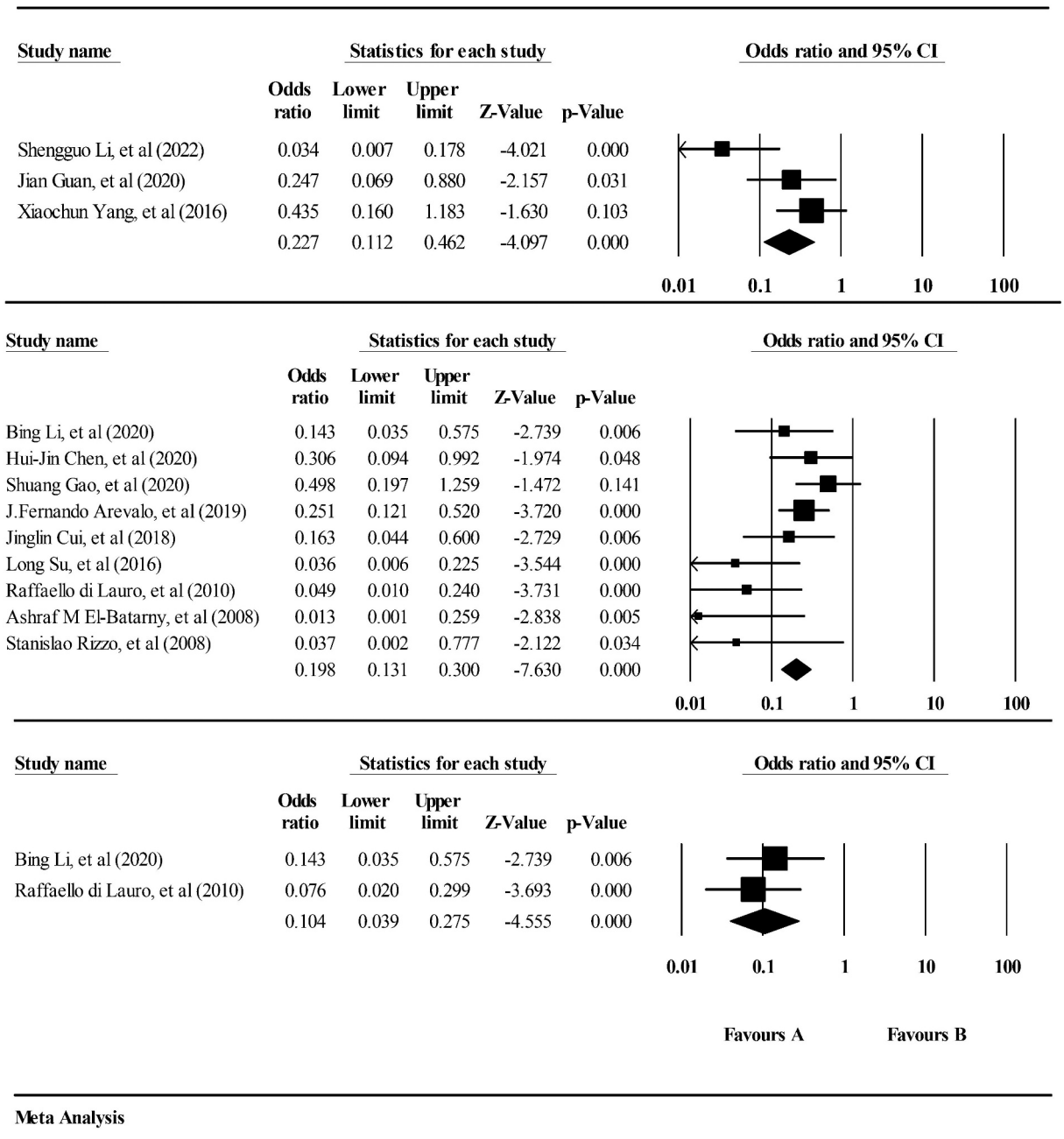

Figure 3. Comparison of intraoperative bleeding as one of the criteria for the efficacy of adjuvant intravitreal injection of Anti-VEGF on the results of PPV for TRD in diabetic patients in 3 studies groups, injection.

3.4. Requirement of relaxing retinotomy

According to the studies, the available data for the necessity for relaxing retinotomy in the two groups, injection 72 hours and 7–21 days before surgery, were limited. Nevertheless, based on statistical analysis, firstly, in all three groups, the need for relaxing retinotomy during surgery was significantly lower than the control group (without adjuvant anti-VEGF injection), and secondly, in the injection group 72 hours before surgery, the requirement of relaxing retinotomy was lower than the other two groups (OR: 0.195, 0.042–0.896, p: 0.036) (Figure 6).

3.5. The need to inject so as endocular tamponade

According to the studies, the available data for the requirement of SO usage as endocular tamponade in two groups, injection 72 hours and 7–21 days before

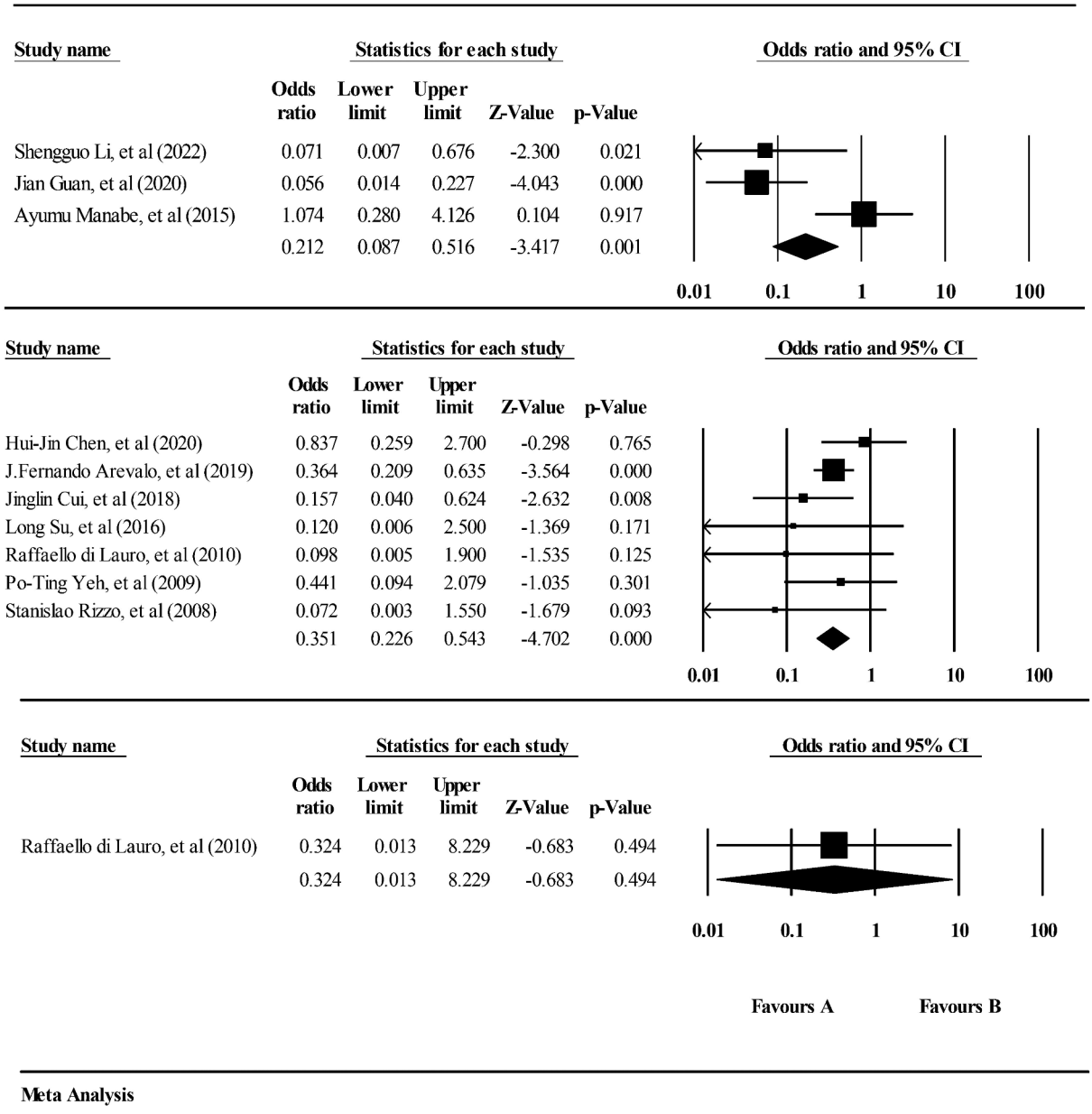

Figure 4. Comparison of iatrogenic retinal break creation as one of the criteria for the efficacy of adjuvant intravitreal injection of anti-VEGF on the results of PPV for TRD in diabetic patients in 3 studies groups, injection.

surgery, was limited. Nevertheless, based on the statistical analysis, firstly, in all three groups, the rate of SO injection was significantly lower than the control group (without anti-VEGF adjuvant injection), and secondly, in the injection group 7–21 days before surgery, the need for SO ocular tamponade was less than the other two groups (OR: 0.076, 0.020–0.299, p: 0.000) (Figure 7).

4. Discussion

Intravitreal VEGF inhibitors paved the way for advances in the management of PDR, and in last decades, many reports have represented that the application of anti-VEGF agents as an adjunctive therapy before the PPV would significantly diminish intraoperative bleeding and the other complications, consequently improving the surgical outcomes. Recently, the effectiveness of preoperative intravitreal anti-VEGF has been widely verified. It has been proved that adjuvant anti-VEGF before PPV, in addition to improving visual prognosis, has reduced the duration of surgery and its complications. The purpose of preoperative intravitreal VEGF inhibitors is to induce the regression of retinal neovascularization, decrease the intraoperative hemorrhage, and facilitate easier fibrovascular membrane dissection and smoother vitrectomy. However, there are

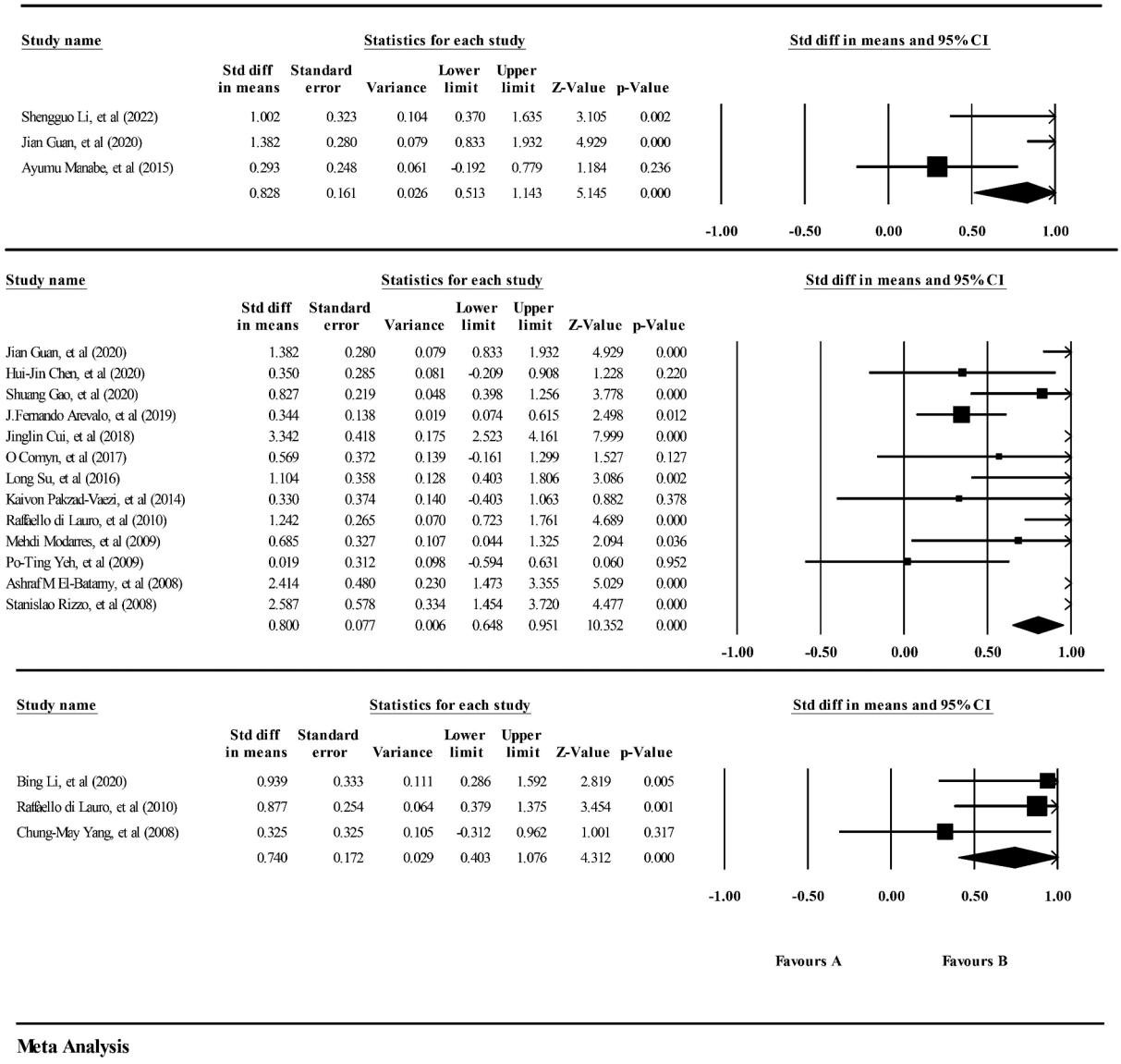

Figure 5. Comparison of surgical time as one of the criteria for the efficacy of adjuvant intravitreal injection of Anti-VEGF on the results of PPV for TRD in diabetic patients in 3 studies groups, injection.

some concerns regarding side effects, especially the progression of fibrosis and tractional complications. Li et al in a RCT in 2015 investigated the effect of intravitreal Bevacizumab (IVB) on vitreous-retinal surface fibrosis in PDR patients before PPV and compared three groups including two groups with injection 5 days and >2 weeks before surgery and a group without injection [54]. They reported the degree of vitreoretinal fibrosis was significantly increased in subgroups with injection >2 weeks before surgery compared to subgroups with injection 5 days before surgery and to patients that did not receive IVB. Also, they found that basic fibroblast growth factor (bFGF) levels increase in PDR patient's vitreous after IVB treatment longer than two weeks prior to surgery and correlated with the degree of fibrosis after IVB. The results of such studies raised concerns regarding the appropriate time of injection before surgery to prevent tractional complications. Based on these concerns about progression of TRD by anti-VEGF agents which has been raised by other researchers [55,56], some authors suggested performing the injection with a short interval like 1–3 days [50,51]. However, others recommended the injection with an interval of more than 2 weeks [36,57], in order to make full use of anti-VEGF and induce the complete regression of retinal neovascularization. Castillo J et al in a RCT in 2017 on 56 patients with PDR-related complications requiring PPV reported subjects received preoperative IVB 5–10 days before surgery had better outcomes compared to 1–3 days based on BCVA at 6 months follow-up, intraoperative and postoperative complications [25].

Currently, controversies regarding the optimal time point of adjuvant anti-VEGF before PPV for PDR still exist. This meta analysis showed that preoperative intravitreal VEGF inhibitors reduce the surgical time, achieve fewer iatrogenic retinal

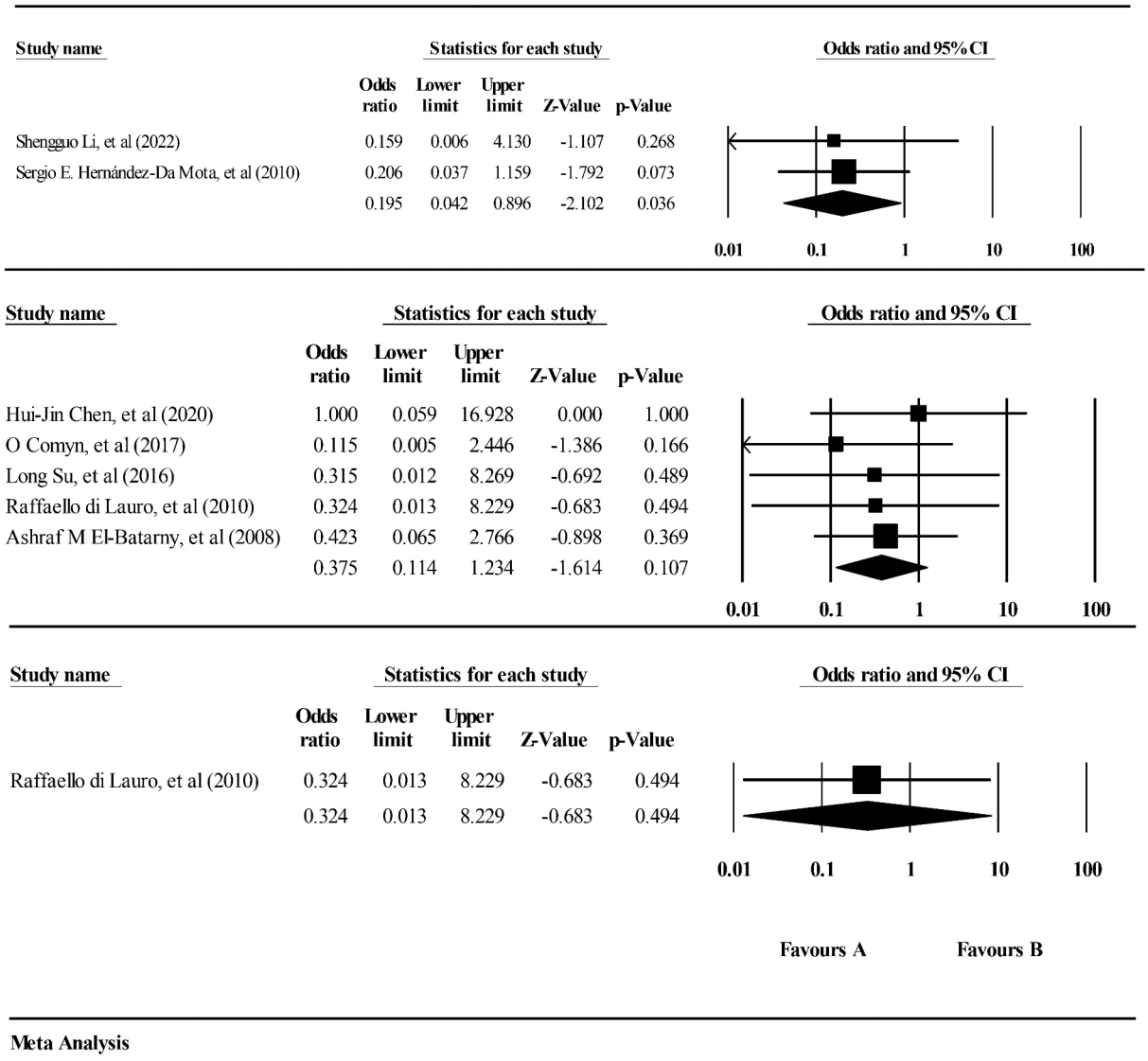

Figure 6. Comparison of relaxing retinotomy necessity as one of the criteria for the efficacy of adjuvant intravitreal injection of Anti-VEGF on the results of PPV for TRD in diabetic patients in 3 studies groups, injection.

breaks and subsequently reducie the need for SO tamponade, and lessen intraoperative hemorrhage. The study proved the lowest risk of intraoperative hemorrhage, the minimum duration of surgery, and the lowest need for SO tamponade was in the injection group 7–21 days before surgery; however, the rate of iatrogenic retinal break during surgery and the necessity for relaxing retinotomy in the injection group 72 hours before surgery was lower than the other two groups.

5. Conclusion

Although, the appropriate timing for injection differ for the variables measured, this study provides valuable consensus on the management of PDR and should help guide the vitreoretinal surgeons in clinical decision making. The authors suggested to inject anti-VEGF within 3 days before PPV to prevent tractional complications. However, it is recommended to conduct more multi-center clinical trials with a large statistical population, taking into account confounding factors and more precise time intervals, and of course, by examining the different types of Anti-VEGF, which are available for a more detailed findings.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

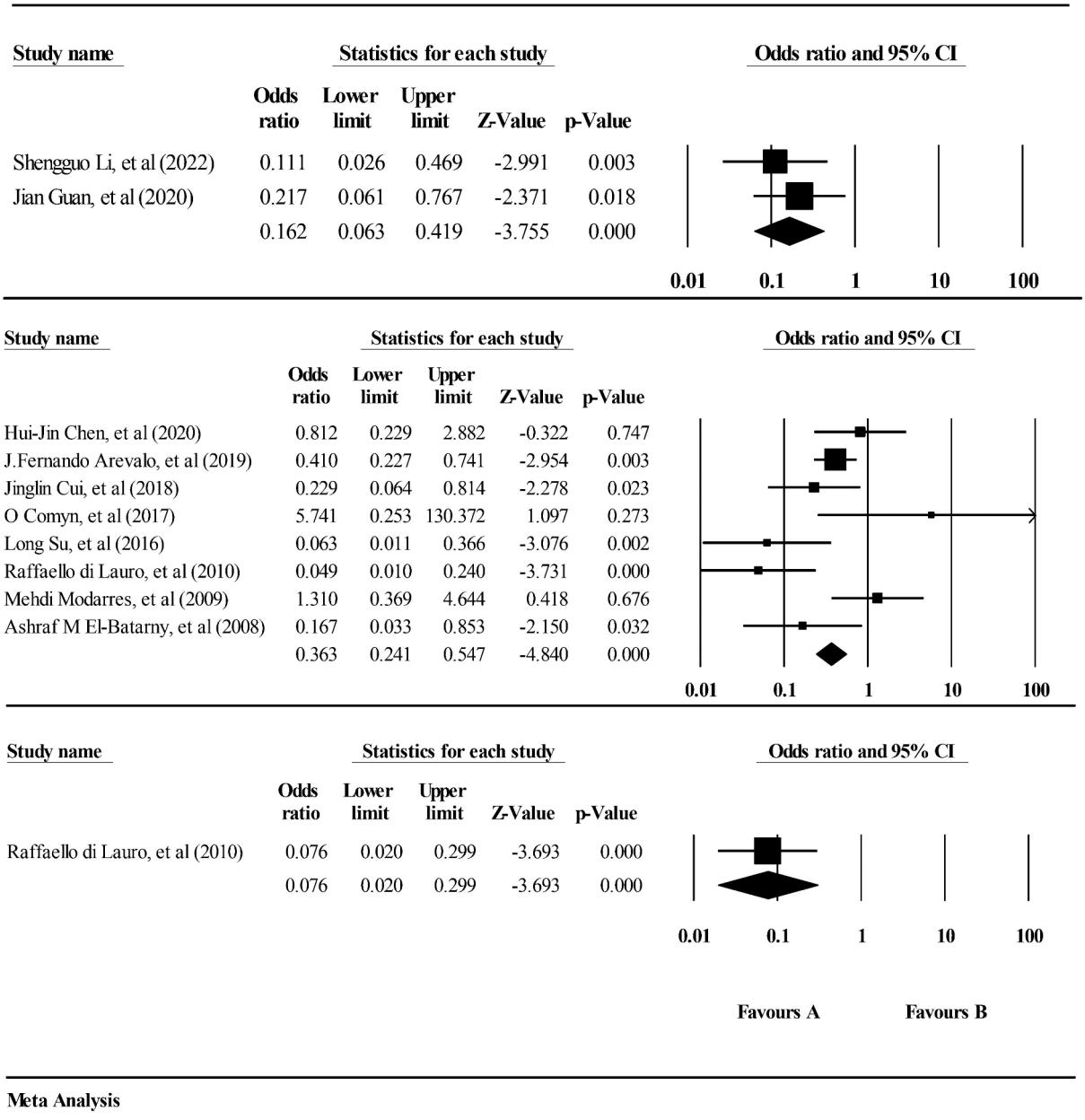

Figure 7. Comparison of so tamponade requirement as one of the criteria for the efficacy of adjuvant intravitreal injection of Anti-VEGF on the results of PPV for TRD in diabetic patients in 3 studies groups, injection.

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