Int Ophthalmol (2024) 44:37
https://doi.org/10.1007/s10792-024-02983-4

REVIEW

Endophthalmitis following same-day bilateral anti-VEGF injections: a systematic review

Jakob Bjerager · Javad Hajari · Oliver Niels Klefter · Yousif Subhi · Miklos Schneider

Received: 4 September 2023 / Accepted: 29 October 2023

Abstract

Purpose To review the risk of endophthalmitis in same-day bilateral anti-VEGF injections.

Methods We searched 12 literature databases for studies on the risk of endophthalmitis after same-day bilateral intravitreal anti-VEGF injections. Data extraction was made independently by two authors and discussed afterward until reaching consensus.

Results Seventeen studies were included with a total of 138,478 intravitreal anti-VEGF injections (69,239 bilateral injections sessions) given in at least 7579 patients. In total, 33 cases of endophthalmitis had occurred, and no cases were bilateral. The incidence of endophthalmitis ranged from 0 to 0.53% per intravitreal injection across studies.

Conclusions We suggest that clinicians can consider same-day treatment of both eyes of patients in need of bilateral intravitreal anti-VEGF injection therapy, but larger studies are needed to quantify the exact risk of endophthalmitis.

Keywords Bilateral · Same-day · Same-session · Intravitreal · Injection · Anti-VEGF · Risk · Adverse event · Endophthalmitis · Systematic review

Introduction

Intravitreal injections with anti-VEGF agents have drastically improved visual outcomes in patients with various exudative retinal diseases [1]. The use of such injections is increasing globally, in part due to higher prevalence of retinal diseases in aging populations, which greatly increases the number of patients needing therapy [2, 3]. Most patients need regular injections, typically every 4 to 16 months, depending on the type of anti-VEGF and the patient's response to the treatment [4]. Patients with age-related macular degeneration (AMD) report an average total time of 12 h per visit including post-appointment recovery, and caregivers need to take time away from work to accompany patients for more than 20% of care visits [5]. Intuitively, patients who need bilateral intravitreal injection treatment can halve the personal cost and

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10792-024-02983-4.

J. Bjerager · J. Hajari · O. N. Klefter · Y. Subhi · M. Schneider (✉)
Department of Ophthalmology, Rigshospitalet Glostrup, Valdemar Hansens Vej 1-23, 2600 Glostrup, Denmark
e-mail: miklos.schneider@regionh.dk

O. N. Klefter
Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Y. Subhi
Department of Clinical Research, University of Southern Denmark, Odense, Denmark

M. Schneider
Department of Ophthalmology, Semmelweis University, Budapest, Hungary

Published online: 08 February 2024

time spent for visits by receiving same-session bilateral injections compared to injections given in each eye on different dates. It is therefore not surprising that more than 90% of patients express a strong preference for same-session bilateral injections over separate, unilateral injection sessions [6]. Third parties benefit accordingly, as salary or leisure time opportunity cost of caregivers are reduced, and potentially reimbursed transportation costs are halved. Moreover, bilateral injection treatment decreases the patient turnover in clinics, which reduces the administrative complexity and enhances the clinical efficiency of treatment centers. Less contacts with health care services have also been a priority during the COVID-19 pandemic.

Serious complications of anti-VEGF injection therapy are generally rare, with the most feared ocular adverse event being endophthalmitis, occurring less than once in 3500 cases [7]. Nevertheless, in bilateral same-session injection therapy, a worst-case scenario is that patients get blind due to severe adverse events occurring in both eyes simultaneously [8], which has been described in singular case reports due to endophthalmitis [9].

In order to reliably investigate the risk of such rare events, very large study populations are needed [8]. For this reason, we have performed a systematic review of the literature to evaluate the risk of endophthalmitis after same-session bilateral intravitreal anti-VEGF injection therapy.

Materials and methods

Study design

This study was a systematic review designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The recommendations of the Cochrane Handbook [10] were followed. According to Danish law, institutional review board approval is not required for such studies. The study protocol was prospectively registered in the PROSPERO database (registration ID: CRD42023405319).

Eligibility criteria

Studies were considered when fulfilling the following criteria:

- *Population*: Patients ≥ 18 years of age, being treated with intravitreal injection therapy. No further restrictions on the definition of study participants were enforced.
- *Exposure*: Studies were considered in which any kind of anti-VEGF therapy was administered bilaterally in the same setting. If studies did not provide clear statements regarding the timing and setting of injections, it was assumed that studies investigating 'same-day,' 'same-setting,' or 'bilateral' injection therapy had analyzed bilateral injections administered in immediate succession during the same patient sitting. Studies that included intravitreal injections with corticosteroids or antibiotics were excluded due to different drug properties and the potential of dissimilar underlying mechanisms of the diseases being treated, as compared to those treated with anti-VEGF. We did not restrict to any practical aspects of the intravitreal injection, such as the setting (e.g., operating theater or office), the personnel (e.g., doctor or nurse), the device (e.g., prefilled syringes, injection assisting devices, or gauge-size), the underlying retinal condition, or the injected agent (ranibizumab, aflibercept, brolucizumab, bevacizumab, faricimab, or conbercept).
- *Outcome:* The aim was to investigate the incidence of post-injection endophthalmitis defined as infectious endophthalmitis. It was assumed that studies investigating or mentioning endophthalmitis without further details were referring to infectious and not sterile endophthalmitis.
- *Study types:* All prospective and retrospective studies were eligible for inclusion, regardless of any of the following study designs: randomized controlled trials, observational studies, case–control studies, cohort studies, or cross-sectional studies. We did not consider single case studies or case series.

Information sources and search strategy

One trained author (Y.S.) searched the literature databases PubMed, EMBASE, Cochrane Central, Web of Science Core Collection, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, SciELO Citation Index, Cumulative Index to Nursing and Allied Health Literature and Zoological Record. No date restrictions were enforced. Studies were considered if disseminated in English or German. Details of the search strategies across literature databases were specified and documented in relation to the search (**Supplementary file 1**). The search took place on February 26th, 2023. References of studies eligible for inclusion were screened for additional relevant studies.

Study selection, data collection, and risk of bias within studies

One author (J.B.) examined titles and abstracts from the literature search and removed duplicates and obviously irrelevant reports. Two authors (M.S. and J.B.) then independently examined full text of remaining references for eligibility and reviewed references from these studies for any additional relevant studies. Afterward, consensus was attempted within the study group and in case of further disagreement, a third author (Y.S.) was invited to discuss and to reach a final consensus. Data regarding study design, characteristics, methods, and results were extracted from eligible studies using extraction forms.

To assess the quality of the studies, the Newcastle–Ottawa Quality Assessment Scale (NOS) for Cohort Studies toolkit was used, which evaluates categories within three domains: selection, comparability, and outcome. Categories within selection are representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at start of study. For comparability, one category evaluated is comparability of cohorts on the basis of the design or analysis. Categories within outcome are assessment of outcome, whether follow-up long enough for outcomes to occur, and adequacy of follow-up of cohorts. 0–2 points are given comparability criteria while 0–1 points are given for other criteria. The quality score of 0–9 is a summary of the number of points across all categories within each study. The risk of bias assessment was conducted by two authors (O.K. and J.B.) independently. In case of disagreement, a third author (Y.S.) was invited to reach consensus.

Synthesis of results

All studies were reviewed qualitatively in text and tables. Total single injections, total bilateral injection sessions, and mean injections per patient were recorded from study publications if stated or was otherwise calculated if the data was available. It was assumed that one bilateral injection equaled two single injections if no other information was provided. Incidence of endophthalmitis was calculated from studies that presented either positive or negative statements on the occurrences of endophthalmitis, or if it was otherwise obvious that the investigators had been attentive to endophthalmitis but found no cases.

Results

Study selection

The literature search found 3,324 titles and abstracts, of which 1,616 duplicates and 1,676 obviously irrelevant reports were discarded. Thirty-two remaining publications were reviewed in full-text, 15 of which were discarded for reasons: not original data ($n=5$), reporting on injections of both anti-VEGF and triamcinolone injections ($n=3$), bilateral injections not performed during the same session ($n=3$), case report ($n=1$), published in neither English nor German ($n=2$), or pre-publication conference abstract of an already included study ($n=1$). Consequentially, 17 studies were found eligible for inclusion (Fig. 1), which summarized data of 138,478 intravitreal anti-VEGF injections (69,239 bilateral injections sessions) [6, 8, 11–25]. In one study, the exact number of injections was not disclosed, but 87 patients had bilateral same-session injections during a 1-month long study period, from which we interpret that 174 injections (87 bilateral injection sessions) were given [25]. No additional studies were found from screening references of included studies.

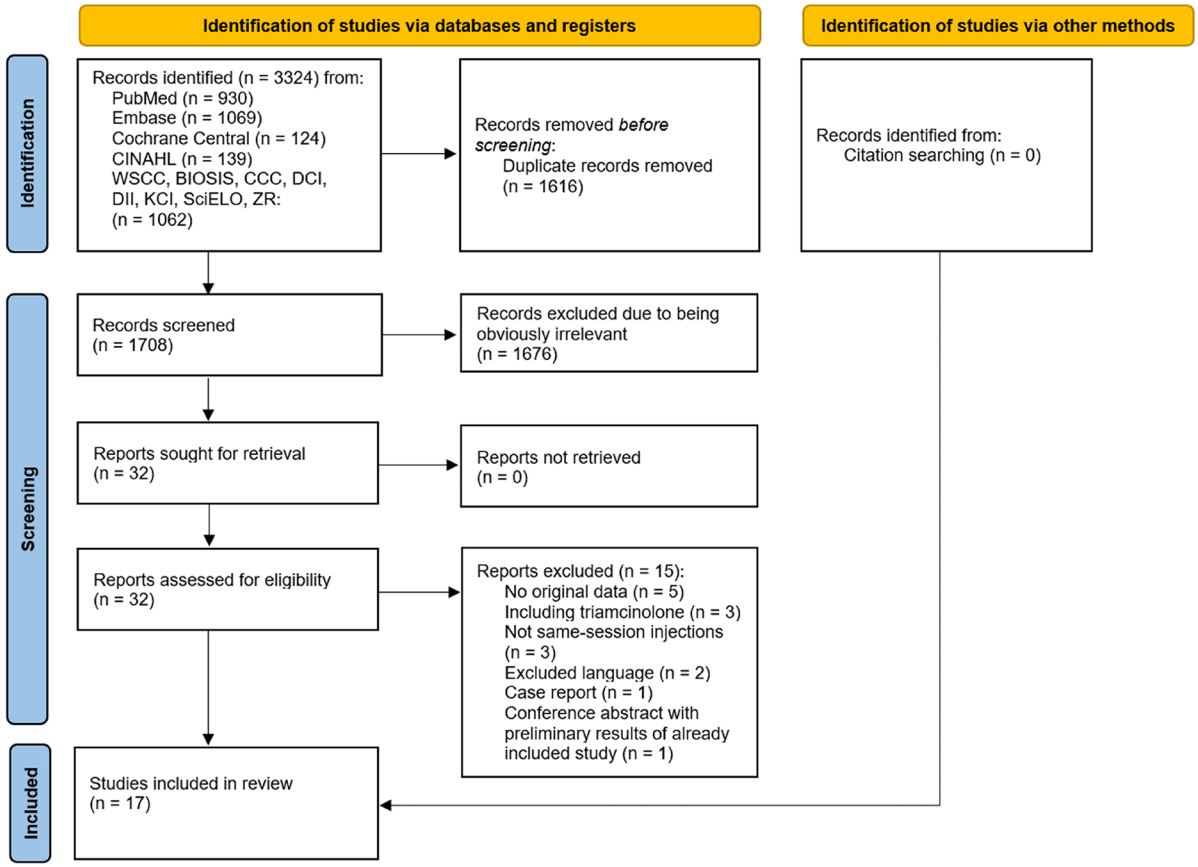

Fig. 1 PRISMA 2020 flow diagram for systematic reviews which includes searches of databases, registers, and other sources. *WSCC* Web of science core collection, *BIOSIS* BIOSIS previews, *CCC* Current contents connect, *DCI* Data citation index, *DII* Derwent innovations index, *KCI* KCI-Korean journal database, *SciELO* SciELO citation index, *ZR* Zoological record

Study characteristics

Fifteen studies were of retrospective nature, with all but one [20] being clearly defined as single-center and register-based, while two were prospective, randomized clinical trials [15, 25]. Eight studies originated from the USA [6, 8, 13, 15, 18, 19, 21, 24] and the rest from Lithuania [20], the UK [22], Jordan [23], France [25], Nigeria [11], Spain [12], Canada [14], South Korea [16], and Pakistan [17]. The studies were published between 2009 and 2022 examining injections administered between 2006 and 2019. (Table 1).

The highest number of injections came from the study by Borkar et al. with 101,932 total single injections (50,966 bilateral injection sessions) followed by Jeeva et al. with 15,338 injections. Five studies contributed between 1,000 and 10,000 injections [12, 14, 16, 18, 19] and the remaining studies included less than one thousand injections each [6, 11, 13, 15, 20–25]. In total, at least 7579 patients were included (two studies did not disclose the number of patients [12, 17]). Among studies that disclosed the number of included patients, Borkar et al. had the largest study with 5,890 subjects, followed by Lima et al. and Jang et al. with 367 and 323 patients, respectively. Five studies included between 100 and 300 patients [6, 14, 19] and the remaining studies included less than 100 patients each.

The age of participants was disclosed in 10 studies [6, 8, 11, 13–16, 19, 21, 22]. The mean age of patients ranged from 55.7 to 82.5 years across these studies.

Table 1 Study demographics

Reference	Country	Design	Population	Demographics
Lima et al. 2009	USA	Retrospective, register-based single-center study	All bilateral intravitreal injections performed between January 6, 2006, and June 1, 2009	3,068 total injections (1,534 bilateral injection sessions) in 367 patients
Davis et al. 2010	USA	Retrospective, register-based single-center study	Same-day injections of either ranibizumab or bevacizumab between January 1, 2007, and July 1, 2008	1,322 total injections (661 bilateral injection sessions) in 127 patients (66.1% female), mean age 82.5 years (median = 83, range = 56–101) Mean no. of previous total injections per patient: 10.4 Mean follow-up: 14.2 months (range 1–26)
Mahajan et al. 2011	USA	Retrospective, register-based single-center study	Consecutive group of patients with AMD who received bilateral intravitreal anti-VEGF injections between January 2006 and November 2008. Any patient with fewer than 4 months of follow-up after their last recorded injection was excluded	904 total injections (452 bilateral injection sessions) in 102 subjects (57.8% female; average age 81.1 years, SD 7.2 years, range 53–98 years) Mean no. of previous total injections per patient: 8.8 (range 2–26)
Cimbalas et al. 2012	Lithuania	Retrospective study	Patients with neovascular AMD who received bevacizumab injections in both eyes simultaneously	65* total injections (32.5* bilateral injection sessions) in 36 patients Mean no. of previous total injections per patient: 2.5 (range 1–10) Mean follow-up: 19.1 months (range 6–44)
Gregori et al. 2012	USA	Prospective, randomized clinical trial	Among patients requiring frequent injections, those patients who received at least three prior intravitreal injections were included	38 total injections (19 bilateral injection sessions) in 19 subjects (100% male; mean age 76 years (SD 13 years)) Mean number of previous total injections per patient: 22 (SD 17) Mean follow-up: approximately 1 month
Shah et al. 2012	UK	Retrospective, register-based single-center study	Patients who received same-day consecutive bilateral IVT ranibizumab for nAMD treatment under the care of one consultant were retrospectively identified over 3 months and followed up for 41 months (February 2007–June 2010)	190 total injections (95 bilateral injections sessions) in 25 patients (48% male, mean age 80 years (range: 65–88, SD: 5.71) Mean no. of total injections per patient: 7.6 (range: 2–28, SD: 7.82) Mean follow-up: 41 months
Abu-Yaghi et al. 2014	Jordan	Retrospective, register-based single-center study	Patients who underwent bilateral intravitreal injections performed between September 2010 and September 2013	684 total injections (342 bilateral injections) in 74 patients Mean no. of total injections per patient: 9.24 (range 4–40, SD 2.80) Mean follow-up: 22 months (range 6–36)

Table 1 (continued)

Reference	Country	Design	Population	Demographics
Chao et al. 2014	USA	Retrospective, register-based single-center study	Bilateral injections given between October 2007 and May 2013	660 total injections (330 bilateral injection sessions) in 79 patients Mean no. of total injections per patient: 8.4 (range 2–62) Mean follow-up: 26 months (range 1–66)
Giocanti-Auregan et al. 2016	France	Prospective, multicenter study	All consecutive patients who received an intravitreal injection of anti-VEGF over a 1-month period (July 1 to 31, 2014)	At least 174 total injections in 87 patients (56.3% female)
Okoye et al. 2016	Nigeria	Retrospective, register-based single-center study	All patients receiving bilateral anti-VEGF injections from March 2013 to March 2015	442 total injections (221 bilateral injection sessions) in 63 patients (Mean age 55.7 ± 15.6 SD years, 41.7% female) Mean no. of total injections per patient: 7.02 Mean follow-up: 40.6 ± 13.1 SD days (range: 1–364 days)
Ruão et al. 2018	Spain	Retrospective, register-based single-center study	Bilateral same-day anti-VEGF injections conducted between January 2011 and March 2016	1,612 total injections (806 bilateral injection sessions); number of patients not stated
Bagheri et al. 2018	USA	Retrospective, register-based single-center study	All patients that received same-session bilateral intravitreal anti-VEGF injections between January 15, 2009, and May 16, 2017	732 total injections (366 bilateral injections sessions) in 73 patients (52.1% female, median age 65 ± 16.29 (range, 22–95) years Median no. of total injections per patient was 7 ± 8.63 (range, 1–54) Median follow-up period was 1185 ± 787 (range, 49–3008) days
Borkar et al. 2018	USA	Retrospective, register-based single-center study	All bilateral same-day intravitreal anti-VEGF injections performed between April 1, 2012, and August 21, 2017. Cases in which additional procedures were performed in the post-injection period, such as glaucoma or cataract surgery, were excluded	101,932 total injections (50,966 bilateral injection sessions) in 5890 patients (mean age 74.2 years (SD 14.1), 60.6% female) Mean no. of total injections per patient: 17.31

Table 1 (continued)

Reference	Country	Design	Population	Demographics
Juncal et al. 2019	Canada	Retrospective, register-based single-center study	Patients who had received bilateral same-day intravitreal anti-VEGF injections between January 1, 2016, and December 31, 2016. If any of the identified patients were receiving simultaneous bilateral injections on a regular basis prior to 2016, data pertaining to these previous injections and follow-ups were also included	9,798 total injections (4,899 bilateral injection sessions) in 262 patients (mean age 76.8 ± 11.1 years, 57.6% female) Mean no. of total injections per patient: 37.4 ± 28.2 (range 2–142) Mean follow-up: 27.4 ± 18.8 months (range 1–76)
Ali et al. 2020	USA	Prospective, single-center, randomized clinical trial	Patients aged more than 18 years who required bilateral IVI in anti-VEGF therapy from May 2018 to September 2018. Subjects were excluded if they had allergy, infectious keratitis, unilateral contact lens wear or known corneal epitheliopathy	100 total injections (50 bilateral injections sessions) in 50 patients (mean age 68 ± 12.9 years (range 39–92), 40% female Mean no. of total injections per patient: 2 Follow-up: 1 day
Jang et al. 2020	South Korea	Retrospective, register-based single-center study	Patients who received intravitreal anti-VEGF injection in both eyes on the same day between January 2014 and June 2019	1418 total injections (709 bilateral injections sessions) in 323 patients (average age was 62.47 ± 13.97 years, 41.8% female) Mean no. of total injections per patient: 4.39
Jeeva et al. 2022	Pakistan	Retrospective, register-based single-center study	Patients who had received aflibercept, bevacizumab and/or ranibizumab from March 1, 2008, to February 28, 2018	15,338 total injections (7,669 bilateral injections sessions) Mean no. of total injections per eye: N/A Follow-up: Within 1 week

AMD Age-related macular degeneration, *anti-VEGF* Anti-vascular endothelial growth factor, *IVT* Intravitreal therapy, *nAMD* Neovascular AMD, *SD* Standard deviation

*Available data could not uncover whether 64 or 66 injections had been given

Neovascular age-related macular degeneration was the sole indication for injection therapy in four studies [6, 19, 20, 22] and the primary indication for treatment in six studies [8, 14, 16, 18, 21, 25], while diabetic macular edema was the primary indication in four studies [11, 13, 15, 23]. Three studies did not disclose either the indications or the number of patients with certain indications for treatment [12, 17, 24] (Table 2).

Details of injections

Seven studies investigated injections with bevacizumab, ranibizumab, and aflibercept [8, 13–17, 24]. Three studies examined ranibizumab and bevacizumab injections [6, 18, 19, 23] and one study included ranibizumab and aflibercept [12]. The three remaining studies were with bevacizumab only [11, 20] or ranibizumab only [21, 22] or without disclosure of the type of anti-VEGF agent [25]. Excluding the three studies that did not reveal the relative number of injected agents [13, 19, 25], 52.2% of total injections across all studies were ranibizumab, 28.6% were aflibercept and 25.6% bevacizumab.

Injections were given by ophthalmologists [11–13, 19], consultants [11, 22, 23], an unspecified treating physician [21], qualified or trained ophthalmology residents [11, 23], physicians in training under direct supervision of retina specialists [24], vitreoretinal fellows or specialists [8, 14] or a vitreoretinal fellowship trained retinal specialist [8], while 6 studies provided no information regarding proceduralists (Table 3).

Injection technique was specified in 14 studies. In 7 studies it was explicitly stated that injections were delivered according to local or national standard protocols [13, 17–19, 22, 24]. The injection setting was provided by 8 studies and was office-based [8, 14, 18], a dedicated outpatient or treatment room [16, 22], ophthalmic operating room [17, 23], or a controlled ambient surgery cabin [12]. All but two studies specified that a new set of sterile equipment was used for each eye, but exact details varied. In one study, the same bottle of anesthetic and disinfectant was used for fellow eyes [8]. In two studies, masks and gloves were not used by physicians, but silence was maintained during injections [8, 12]. Topical anesthesia included topical drops and/or application of cotton swabs soaked in an anesthetic agent administered once or several times and/or subconjunctival injections. In studies that disclosed the information, lid speculum was always used in 8 studies, never used in 2 studies [8, 15] and mostly used in one study [14]. Povidone-iodine was the ocular disinfectant used in all but one study, which was a clinical trial on aqueous chlorhexidine and povidone-iodine [15]. Disinfection of the periorbital skin and eyelids was done in 6 studies [11, 16, 17, 19, 21, 23]. Across the studies, 30-, 31- or 32-gauge needles were used, and anti-VEGF injections were drawn from single-use vials or came as prepacked syringes from compounding pharmacies. Only one study stated explicitly that anti-VEGF injections for fellow eyes came from different batch numbers [17]. Injection sites were mostly specified as 3–4 mm posterior to the limbus, and the distance was measured by caliper in four studies [6, 11, 17, 21]. After injection, a sterile cotton tip was applied to the injection site in four studies [6, 11, 14, 21], and in most studies topical antibiotics were prescribed, ranging from fluoroquinolone [6, 11, 12, 16–19, 23] or Polymyxin B and Trimethoprim [18] to chloramphenicol [22]. (Table 3).

Risk of bias within individual studies

Newcastle–Ottawa Scale study quality scores were generally mediocre, mainly due to the lack of control groups (9 studies; Selection item #2) and inadequate or no comparability between intervention and control groups (15 studies; Comparability item). Lack of adequate follow-up time for the outcome of endophthalmitis to occur (Outcome item #2) and no statements on whether loss to follow-up had occurred (Outcome item #3) also negatively impacted quality scores for one-third of studies. The highest quality score was found for Mahajan et al. [6] with a quality score of 8, while Lima et al. [18], Cimbalas et al. [20], and Okoye et al. [11] were given the lowest score of 4 (Table 4). We choose to grade studies equally regarding Selection item #4 (‘demonstration that outcome of interest was not present at start of study’) and give all studies a point, due to the following reasons: It is unlikely for patients to have had endophthalmitis before injections, and we consider it common practice to cancel scheduled injection treatment or reassess patients if they present with obvious clinical signs of endophthalmitis.

Table 2 Therapy details and study outcomes

Reference	Indication for intravitreal treatment	Types and numbers of total intravitreal injections given (%)	Cases of endophthalmitis reported n (% of total injections)
Lima et al. 2009	nAMD: 96.5%; PDR: 1.6%; MTT2: 0.8%; CRVO: 0.5%; BRVO: 0.3%; IGS: 0.3%	Bevacizumab: 652 (21.3%) Ranibizumab: 2,416 (78.7%)	2 (0.065%); both unilateral; both after ranibizumab
Davis et al. 2010	nAMD: 100.0%	Bevacizumab: N/A Ranibizumab: N/A	0
Mahajan et al. 2011	nAMD: 100.0%	Bevacizumab: 412 (45.6%) Ranibizumab: 412 (45.6%) Bevacizumab/ranibizumab Combination: 80 (17.7%)	0
Cimbalas et al. 2012	nAMD: 100.0%	Bevacizumab: 65 (100.0%)	0
Gregori et al. 2012	nAMD: 78.9% DME: 21.1%	Ranibizumab: 38 (100.0%)	0
Shah et al. 2012	nAMD: 100.0%	Ranibizumab: 190 (100.0%)	0
Abu-Yaghi et al. 2014	DME: 95.9%; nAMD: 4.1%	Bevacizumab: 668 (97.7%) Ranibizumab: 16 (2.3%)	1 (0.29%); unilateral; after bevacizumab
Chao et al. 2014	N/A	Bevacizumab: 282 (42.7%) Ranibizumab: 281 (42.6%) Aflibercept: 97 (14.7%)	0
Giocanti-Auregan et al. 2016	nAMD: 51 (58.6%); DME: 34 (39.1%); Vasoproliferative tumor: 2 (2.3%)	Not disclosed	0
Okoye et al. 2016	DME: 36.5%; PDR: 28.6%; PCV: 11.1%; nAMD: 6.3%; BRVO: 1.6%; CNV: 1.6%; CRVO: 1.6%; HR: 3.2%; PSCR: 3.2%; mCNV: 1.6%; NPSCR: 1.6%; Pseudophakic macular edema: 1.6%; Rubeotic glaucoma: 1.6%	Bevacizumab: 100%	0
Ruão et al. 2018	nAMD: N/A; DR: N/A; RVO: N/A; mCNV: N/A	Ranibizumab: 1,495 (92.7%) Aflibercept: 117 (7.3%)	0
Bagheri et al. 2018	DME: 54.8%; nAMD: 37.0%; RVO: 5.5%; Other: 2.7%	Ranibizumab: N/A Aflibercept: N/A Bevacizumab: N/A	0
Borkar et al. 2018	nAMD: 54.3%; DME: 35.4%; RVO: 4.1%; Other: 1.7%; Missing: 4.6%	Ranibizumab: 55,051 (54.0%) Aflibercept: 32,542 (31.9%) Bevacizumab: 14,339 (14.1%)	28 (0.027%); all unilateral
Juncal et al. 2019	nAMD: 65.5%; DME: 32.9%; PPCV: 0.8%; CME: 0.4%; RVO: 0.4%	Ranibizumab: 7,824 (79.9%) Aflibercept: 1,860 (19.0%) Bevacizumab: 114 (1.1%)	1 (0.010%); unilateral
Ali et al. 2020	DME: 29 (58.0%); nAMD: 18 (36.0%); CRVO: 6.0%	Bevacizumab: 10 (20.0%) Ranibizumab: 30 (60.0%) Aflibercept: 10 (20.0%)	0
Jang et al. 2020	nAMD: 54.8%; DR: 35.3%; RVO: 2.4%; CSCR: 1.3%; Other: 6.2%	Bevacizumab: 1004 (70.8%) Ranibizumab: 178 (12.6%) Aflibercept: 236 (16.6%)	0
Jeeva et al. 2022	N/A	Aflibercept: 560 (3.65%) Bevacizumab: 10,582(68.99%) Ranibizumab: 4,196 (27.36%)	1 (0.0065%); unilateral; after aflibercept

AR Autoimmune retinopathy, *CME* Cystoid macular edema, *DME* Diabetic macular edema, *HR* Hypertensive retinopathy, *IGS* Irvine–Gass syndrome, *IOP* Intra-ocular pressure, *mCNV* Myopic choroidal neovascularization, *MTT2* Macular telangiectasia Type 2, *nAMD* Neovascular age-related macular degeneration, *NPSCR* Non-proliferative sickle cell retinopathy, *PDR* Proliferative diabetic retinopathy, *PPCV* Polypoidal choroidal vasculopathy, *PSCR* Proliferative sickle cell retinopathy, *RVO* Retinal vein occlusion

Table 3 Details of injection procedures

	Proceduralist	Standardized by protocol	Setting	Sterility	Topical anesthesia	Lid speculum	Disinfection	Anti-VEGF agent and needle specifics	Injection site	Post-injection
Lima et al. 2009	–	Yes (local protocol)	Office	Separate syringes for each eye	Proparacaine or tetracaine	–	5% povidone-iodine	31G for bevacizumab; 32G for ranibizumab	3–4 mm posterior to the limbus in inferior quadrants	Polymyxin trimethoprim or ofloxacin 4 times per day for 2 days
Davis et al. 2010	1 ophthalmologist	Yes (local protocol)	–	Separate injections and no drops or equipment reused between eyes	Three rounds 4% lidocaine on sterile aliquot to the inferior fornix and conjunctiva at the injection site after speculum	Yes	10% povidone-iodine for periorbital skin and lashes before speculum and three rounds of 5% povidone-iodine after speculum	–	Pars plana	Topical fourth-generation fluoroquinolone 4 times per day for 4 days
Mahajan et al. 2011	–	–	–	Separate trays of instruments, containers of povidone–iodine, syringes, needles, and sterile gloves	0.1–0.3 mL of 1% lidocaine into the subconjunctival space	Yes	5% povidone–iodine placed onto the conjunctival surface	0.5 mg of ranibizumab or 1.25 mg of bevacizumab injected into the center of the vitreous cavity with a 30G needle	3.5 mm from the limbus marked by calipers	A cotton tip applicator was held at the site of the injection as the needle was withdrawn. One drop of a topical fourth-generation fluoroquinolone 4 times a day for 4 days after the injection
Cimbalas et al. 2012	–	–	–		–	–	–	–	–	–

Table 3 (continued)

	Proceduralist	Standardized by protocol	Setting	Sterility	Topical anesthesia	Lid speculum	Disinfection	Anti-VEGF agent and needle specifics	Injection site	Post-injection
Gregori et al. 2012	One treating physician	Unknown (according to routine technique)		Sterile speculum, cornea wetted or rinsed by polymyxin (after speculum)	Two drops of 0.5% proparacaine and 4% lidocaine or preservative-free 3.5% lidocaine hydrochloride ophthalmic gel (before speculum); three sterile cotton swabs with 4% liquid lidocaine pressed for 60 s each (after speculum; liquid lidocaine group only)	Yes	10% povidone-iodine swab of lids and lashes, 5% povidone-iodine for eye (before speculum); Drops or cotton swabs with 5% povidone-iodine (after speculum); 5% povidone-iodine drop (after calipers)	0.05-ml ranibizumab injection into the vitreous cavity using a sterile 32G needle	Inferotemporal quadrant marked by calipers	Application of sterile cotton swab to injection site
Shah et al. 2012	1 consultant	Yes (national guidelines)	Dedicated enclosed outpatient clean room	Separate sterile gloves, drape, eyelid speculum, mm gauge, syringes, and needles for each eye	Single-use topical anesthetic	Yes	5% povidone-iodine solution applied to the conjunctival sac at least 3 min before injection	Separate vials of ranibizumab 0.5 mg in 0.05 ml for each eye; 30G needle	3.5–4 mm posterior to the limbus	Topical chloramphenicol eye drops four times a day for 4 days
Abu-Yaghi et al. 2014	A consultant or a qualified ophthalmology resident	–	Ophthalmic operating room	Separate sterile speculums, syringes, and needles for each eye	Topical preservative-free oxybuprocaine hydrochloride 0.4% before disinfection; oxybuprocaine hydrochloride 0.4% on the surface of the eyes for approx. 3 min after disinfection	Yes	5% diluted povidone-iodine for periocular area, eyelids, eyelashes, ocular surface, and fornixes	30 or 32G needles. Each bevacizumab vial used for 15 injections. Each ranibizumab vial split into two injections	3.5 mm posterior to the limbus in supertemporal or inferotemporal quadrants	Antibiotic ointment applied; patient given prescription of ofloxacin eye drops 4 times daily for 3 days

Table 3 (continued)

	Proceduralist	Standardized by protocol	Setting	Sterility	Topical anesthesia	Lid speculum	Disinfection	Anti-VEGF agent and needle specifics	Injection site	Post-injection
Chao et al. 2014	Physicians-in-training (n = 11) supervised by retina specialists (n = 2)	Yes (local protocol)	–	No reuse of any instruments or medications between eyes	Prepared and performed by trained technicians (n = 7)	–	–	48% of bevacizumab doses from compounding pharmacy and the rest from commercially available single-use vials for each eye	–	Topical antibiotics in 33% of injections
Giocanti-Auregan et al. 2016	–	–	–	–	–	–	–	–	–	–
Okoye et al. 2016	A consultant, ophthalmologists, and trained residents	–	–	Separate sterile drapes, drops, materials, and instrument for each eye	Topical tetracaine instilled on the eye and fornix and left for approx. 3 min after speculum	Yes	Periorbital skin and eyelashes cleaned separately for each eye with 10% dilute povidone-iodine scrub. After speculum 5% dilute povidone-iodine drops instilled on the eye and fornix and left for approx. 3 min	30 or 32G needles with 1.25 mg/0.05 ml of bevacizumab	Approximately 3.5 mm from the limbus marked by calipers in supertemporal or inferotemporal quadrants	Sterile cotton bud used to tamponade the site of injection after removal needle; paracentesis done; topical second-generation fluoroquinolone (ciprofloxacin) 3 times daily for 5 days
Ruão et al. 2018	Two ophthalmologists	–	Controlled ambient surgery cabin	No surgical scrubs or face mask, but hands washed before each procedure. Silence during injection. Separate sterile needle and syringe for each eye	Topical anesthetic instilled in the conjunctiva and cornea	No	Diluted povidone-iodine instilled in the conjunctiva and cornea	Preparation in laminar flow chamber. 0.05 mL of anti-VEGF given with 30G needle	Sclera 3–3.5 mm from the limbus	Diluted povidone-iodine and ofloxacin ointment
Bagheri et al. 2018	One ophthalmologist	Yes (local protocol)	–	–	–	–	–	–	–	–

Table 3 (continued)

	Proceduralist	Standardized by protocol	Setting	Sterility	Topical anesthesia	Lid speculum	Disinfection	Anti-VEGF agent and needle specifics	Injection site	Post-injection
Borkar et al. 2018	A vitreoretinal fellow or a fellowship trained retina specialist	No	Office	Same bottles of anesthetic and betadine used for fellow eyes	Typically, 2 rounds of topical 0.5% proparacaine or tetracaine hydrochloride to the conjunctiva. Some patients received an additional 1%–2% subconjunctival lidocaine injection	No (bimanual eyelid retraction technique used)	Typically, 2 rounds of 5% povidone-iodine to the conjunctiva. After subconjunctival lidocaine injection another 5% povidone-iodine was instilled	30G or 31G needle. Bevacizumab from prepackaged syringes from compounding pharmacy, aflibercept loaded from single-use vials, ranibizumab either loaded from single-use vials or prefilled	3.0–4.0 mm from the limbus generally in inferotemporal quadrant sometimes with conjunctival displacement	–
Juncal et al. 2019	6 vitreoretinal specialists	No	Office	Separate tray of eye drops and instruments including sterile speculum, syringe and needle used for each eye. Gloves and masks not used but conversation was avoided	Topical tetracaine and sometimes also subconjunctival 1% lidocaine in the quadrant to be injected	Mixed (One physician performed eyelid retraction using a bimanual eyelid retraction technique)	5% povidone-iodine in both eyes following anesthesia and again after speculum was placed	Aflibercept 2.0 mg/0.05 mL from single-use vials. Bevacizumab 1.25 mg/0.05 ml from prepackaged syringes from a compounding pharmacy. Ranibizumab 0.5 mg/0.05 ml either prefilled syringes or from single-use vials. 32G (two physicians) or 30G needles (four physicians). Same or different LOT numbers for fellow eyes	3.5 or 4.0 mm posterior to the limbus in the supertemporal quadrant (5 surgeons) or inferonasal quadrant (1 surgeon)	Cotton tip applicator held at the site of injection as needle was withdrawn, no post-injection antibiotics on a regular basis

Table 3 (continued)

	Proceduralist	Standardized by protocol	Setting	Sterility	Topical anesthesia	Lid speculum	Disinfection	Anti-VEGF agent and needle specifics	Injection site	Post-injection
Ali et al. 2020	–	–	–	–	1 drop of topical 0.5% proparacaine hydrochloride	No (Eyelids held open by an assisting technician)	Right eye randomized to 2 drops (1 drop immediately before injection) of betadine 5% or aqueous chlorhexidine gluconate 0.1% and left eye receiving the opposite	0.05 ml of anti-VEGF with identical injection technique for both eyes, as per the physician's discretion	Identical location between the 2 eyes, as per the physician's discretion	No saline flush, lubricant, or topical anesthetic
Jang et al. 2020	–	–	Independent treatment room	Sterilized fabric covering, new set of instruments and sterile gloves (put on aseptically) for each eye	0.5% proparacaine hydrochloride	Yes	Eyelids and surrounding skin cleaned with cotton swab dipped in 5% povidone iodine solution. Topical 5% povidone iodine solution in eye immediately before injection	Ranibizumab and aflibercept from single-use vials. Bevacizumab from pre-packaged syringes produced through hospital dispensing carried out by skilled doctors and pharmacists in sterile laboratory. 30G needle used	Approximately 3.5–4 mm away from the corneal limbus	Topical Levofloxacin 4 times a day for 1 week
Jeeva et al. 2022	Ophthalmologists	Yes (local protocol)	Operating room	Mask used by all staff. Sterile draping and speculum applied after disinfection. New set of equipment including sterile gloves and speculum for each eye	Proxymetacaine hydrochloride 5% drops in the conjunctiva by trained technician before and after speculum removal	Yes	Eye, eyelids, and lashes cleaned with povidone iodine 5% solution two minutes before procedure	Anti-VEGF for each eye prepared in pharmacy under sterile conditions using different batch numbers for each eye	3.5 mm from limbus for pseudophakic and 4 mm for phakic patients measured by calipers	One drop of moxifloxacin onto the conjunctiva and afterward 4 times a day for 5–7 days at physicians' discretion

Empty fields (-) signifies no information provided. *G* Gauge

Table 4 Study quality of included studies using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies

Reference	Selection				Comparability	Outcome			Quality score
	#1	#2	#3	#4	#1	#1	#2	#3	
	[0–1 ★]	[0–1 ★]	[0–1 ★]	[0–1 ★]	[0–2 ★]	[0–1 ★]	[0–1 ★]	[0–1 ★]	[0–9]
Lima et al. 2009	★	/	★	★	/	★	-	-	4
Davis et al. 2010	★	/	★	★	/	★	★	★	6
Mahajan et al. 2011	★	★	★	★	★	★	★	★	8
Cimbalas et al. 2012	-	★	-	★	★		★	-	4
Gregori et al. 2012	★	★	★	★	-	★	★	★	7
Shah et al. 2012	★	/	★	★	/	★	★	★	6
Abu-Yaghi et al. 2014	★	★	★	★	-	★	★	★	7
Chao et al. 2014	★	★	★	★	-	★	★	-	6
Giocanti-A et al. 2016	★	★	★	★	-		-	-	4
Okoye et al. 2016	★	/	★	★	/	★	-	-	4
Ruão et al. 2018	★	★	★	★	-	★	-	-	5
Bagheri et al. 2018	★	/	★	★	/	★	★	-	5
Borkar et al. 2018	★	/	★	★	/	★	★	★	6
Juncal et al. 2019	★	/	★	★	/	★	★	★	6
Ali et al. 2020	★	/	★	★	/	★	-	★	5
Jang et al. 2020	★	/	★	★	/	★	★	★	6
Jeeva et al. 2022	-	★	★	★	-	★	-	★	5

Categories within three domains are evaluated: selection, comparability, and outcome. Categories within Selection are (#1) representativeness of the exposed cohort, (#2) selection of the non-exposed cohort, (#3) ascertainment of exposure, and (#4) demonstration that outcome of interest was not present at start of study. For Comparability, one category evaluated is (#1) comparability of cohorts on the basis of the design or analysis. Categories within outcome are (#1) assessment of outcome, (#2) was follow-up long enough for outcomes to occur, and (#3) adequacy of follow-up of cohorts. 0–2 stars (points) are given for ascertainment comparability criteria while 0–1 star is given for other criteria. The quality score of 0–9 is a summary of the number of stars across all categories within each study. A dash (–) means that no stars were given. A slash (/) means that no stars were given specifically due to criteria being non-applicable (studies lacking exposure groups)

Incidence of endophthalmitis following bilateral injections

A total of 33 cases of unilateral endophthalmitis were reported after 138,478 injections (69,239 bilateral injections sessions). No cases of bilateral endophthalmitis were seen. The rates of endophthalmitis per single injection in patients receiving bilateral same-session injections ranged from 0.000 to 0.526% (0.526% in the study by Shah et al., 0.146% in Abu-Yaghi et al., 0.065% in Lima et al.; 0.027% in Borkar et al., 0.010% in Juncal et al., 0.007% in Jeeva et al. and zero in the remaining 11 studies).

There were 8 studies that compared an intervention group of patients treated with same-session bilateral injections with a control group of patients treated with unilateral injections, either in one eye only or in both eyes on different dates [6, 12, 17, 20, 21, 23–25]. In total, intervention groups contributed 19,475 same-session bilateral injections, after which two cases of unilateral endophthalmitis had occurred; control groups totaled 31,109 unilateral injections with 7 cases of post-injection endophthalmitis. No cases of bilateral endophthalmitis were described.

Discussion

We have provided a review of the current literature on the risk of endophthalmitis after bilateral same-session intravitreal anti-VEGF injections. Previous meta-analyses on the risk of endophthalmitis after intravitreal injections without specification of treatment laterality have agreed on endophthalmitis rates of 0.05–0.06% [26, 27]. Approximately half this rate was found in the presently largest study on bilateral same-session injections by Borkar et al., which had a sound methodology and contributed to 74%

of injections included in our review [8]. Although a high risk of bias should be acknowledged in such direct comparisons without meta-analysis, it appears that the risk of endophthalmitis after bilateral same-session injections is at a clinically reasonable level.

No cases of bilateral endophthalmitis were reported in any of the studies included in this review. This is reassuring, as endophthalmitis is perceived as the most serious adverse event in intravitreal anti-VEGF injection therapy, after which permanent vision loss is commonly seen, and evisceration may be needed in severe cases [28].

We only considered infectious endophthalmitis in this review, either proven by vitreous cultures [8, 18, 23] or otherwise defined as infectious or presumed infectious [8, 14, 17]. Studies disclosed clear specifics regarding only 4 of the 33 found endophthalmitis cases [14, 18, 23], and group demographics and clinical characteristics were described for 28 additional cases [8]. One study provided limited specifics of endophthalmitis cases, but it was unclear which cases belonged to the groups of unilaterally or bilaterally treated patients [17]. Clear statements of positive vitreous cultures were only present regarding 3 cases, in which of *Streptococcus viridans*, *Staphylococcus epidermidis*, and *coagulase- negative staphylococcus* had been found [18, 23], with antibiotic sensitivity profiles only disclosed for the first two cases [18]. Due to the limited availability of specific microbiological data from these studies, this information is not suitable for preventative purposes.

Several included studies considered cases of sterile inflammation separately from cases of infectious endophthalmitis, heterogeneously defined as sterile vitritis or non-infectious endophthalmitis [11, 19, 22], severe acute intraocular inflammation [18], acute or sterile acute intraocular or ocular inflammation [12, 14, 16], sterile inflammation [6], anterior chamber cell or flare [11, 19], and uveitis [24]. Due to the non-harmonized definitions used, we did not find that a meaningful analysis could be done regarding sterile inflammation.

Despite the lack of large randomized or controlled trials demonstrating safety in bilateral same-session intravitreal injection [25], surveys of intravitreal injection practices among retinal specialists in the USA reveal that the proportion of practitioners that perform bilateral simultaneous injections is high and have remained stable from 2011 to 2019, at approximately 45% [29, 30]. In this systematic review, we found that endophthalmitis is a rare complication following bilateral same-session anti-VEGF injection therapy. Our study found no cases of bilateral endophthalmitis following bilateral same-session injections, which leaves such events to have been described only in rare case reports [9, 31]. Based on a conservative independent risk of endophthalmitis at 0.09% per injection, the risk of bilateral blindness from two independent, sterile procedures should be only 1 in 1.2 million injections [31]. The real-life risk is likely higher, as same-session bilateral procedures will never have a completely detached risk of endophthalmitis, as the treatment room, proceduralists, patient and post-injection patient environment and behavior is the same [31]. In any case, it seems that half of practitioners agree that the convenience and cost benefits of same-session bilateral injections outweigh the clinical risks of such extremely rare, serious patient complications [29, 30]. A prerequisite for acceptance is that injections are treated as separate, sterile procedures, and conducted according to current evidence for endophthalmitis prevention [31].

Other potentially vision-threatening ocular adverse events to anti-VEGF injection therapy include immune-mediated sterile inflammatory reactions, acute increase in intraocular pressure, and retinal detachment [32]. Risk of systemic adverse events, including death, after bilateral anti-VEGF injection therapy has also been a topic of concern [23, 33]; however, evidence so far does not provide a clear direction on this matter. Further studies may be warranted.

Limitations need to be acknowledged regarding this review and its findings. First, our study found that the number of studies and thus total number of bilateral same-session injections published in the literature are limited, and a meta-analysis was not mandated. Findings should therefore not be interpreted as conclusive. Second, lack of homogenous and detailed data across studies, including regarding anti-VEGF drugs, treatment settings and injection providers, did not allow stratified analyses. Finally, since most included studies were retrospective, various sources of bias could have influenced their findings, which may explain the heterogeneity in findings observed across included studies. However, considering the low incidence of endophthalmitis found in this review, even a pragmatic randomized

clinical trial design would need a disproportionally high number of participants and would be challenging to carry out in practice.

Strengths of this study include the literature search strategy including 12 databases, which allowed as many studies as possible to be considered in a comprehensive literature review, as well as adherence to best practice methodology in the study design.

Conclusion

In conclusion, the current literature suggests that the rate of endophthalmitis following bilateral same-session intravitreal anti-VEGF injections is at a clinically acceptable, low level. We suggest that clinicians can consider same-day treatment of both eyes of patients in need of bilateral intravitreal anti-VEGF injection therapy without compromising safety. With an increasing demand for intravitreal therapy, same-day bilateral treatment may hold the potential to improve clinical efficiency and patient satisfaction.

Author's contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JB, YS, ONK, and MS. The first draft of the manuscript was written by JB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declarations

Conflict of interest Author M.S. has received investigator fees from Allergan, Bayer, Novartis, and Roche and has served as an advisory board member for Novartis and Roche and acted as consultant for AbbVie, not related to this work. Author Y.S. declares to have received speakers fee from Bayer and Roche, not related to this work. Other authors declare that no potential conflicts of interests exist in relation to this work.

References

1. Bloch SB, Larsen M (2015) Translational public health care perspective: Intravitreal treatment of neovascular age-related macular degeneration has revolutionized clinical ophthalmology. Acta Ophthalmol
2. Lee AY, Day AC, Egan C, Bailey C, Johnston RL, Tsaloumas MD et al. (2016) Previous intravitreal therapy is associated with increased risk of posterior capsule rupture during cataract surgery. Ophthalmology
3. Williams GA (2014). IVT injections: health policy implications. Rev Ophthalmol
4. Meer EA, Oh DH, Brodie FL (2022) Time and distance cost of longer acting anti-VEGF therapies for macular degeneration: contributions to drug cost comparisons. Clin Ophthalmol 16:4273–4279
5. Prenner JL, Halperin LS, Rycroft C, Hogue S, Williams Liu Z, Seibert R (2015) Disease burden in the treatment of age-related macular degeneration: findings from a time-and-motion study. Am J Ophthalmol 160(4):725–31.e1
6. Mahajan VB, Elkins KA, Russell SR, Boldt HC, Gehrs KM, Weingeist TA et al (2011) Bilateral intravitreal injection of antivascular endothelial growth factor therapy. Retina 31(1):31–35
7. Merani R, Hunyor AP (2015) Endophthalmitis following intravitreal anti-vascular endothelial growth factor (VEGF) injection: a comprehensive review. Int J Retin Vitr 1:9
8. Borkar DS, Obeid A, Su DC, Storey PP, Gao X, Regillo CD et al (2018) Endophthalmitis rates after bilateral same-day intravitreal anti-vascular endothelial growth factor injections. Am J Ophthalmol 194:1–6
9. Tabatabaii A, Ahmadraji A, Khodabande A, Mansouri M (2013) Acute bilateral endophthalmitis following bilateral intravitreal bevacizumab (avastin) injection. Middle East Afr J Ophthalmol 20(1):87–88
10. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VAE (2019) Cochrane handbook for systematic reviews of interventions version 6.3 (updated February 2022). Cochrane,. https://www.training.cochrane.org/handbook. Accessed July 18, 2022
11. Okoye O, Okonkwo O, Oderinlo O, Hassan K, Ijasan A (2016) Bilateral concomitant intravitreal anti-vascular endothelial growth factor injection: Experience in a Nigerian tertiary private eye care facility. Niger J Clin Pract 19(4):544–548
12. Ruão M, Andreu-Fenoll M, Dolz-Marco R, Gallego-Pinazo R (2017) Safety of bilateral same-day intravitreal injections of anti-vascular endothelial growth factor agents. Clin Ophthalmol 11:299–302
13. Bagheri S, Koulouri I, Konstantinou E, Erenler F, Vavvas DG (2018) Visual outcome of bilateral same-session intravitreal anti-VEGF injections. Invest Ophthalmol Vis Sci 59(9):835
14. Juncal VR, Francisconi CLM, Altomare F, Chow DR, Giavedoni LR, Muni RH et al (2019) Same-day bilateral intravitreal anti-vascular endothelial growth factor injections: experience of a large canadian retina center. Ophthalmol J Int d'ophtalmologie Int J Ophthalmol Zeitschrift fur Augenheilkd 242(1):1–7
15. Ali FS, Jenkins TL, Boparai RS, Obeid A, Ryan ME, Wibblesman TD et al (2021) Aqueous chlorhexidine compared with povidone-iodine as ocular antisepsis before intravitreal injection: a randomized clinical trial. Ophthalmol Retin 5(8):788–796

16. Jang K, Ahn J, Sohn J, Hwang DDJ (2020) Evaluation of the safety of bilateral same-day intravitreal injections of anti-vascular endothelial growth factor agents: experience of a large korean retina center. Clin Ophthalmol 14:3211–3218
17. Jeeva IK, Masud S, Siddiqui MAR, Fahad HM (2022) Safety of simultaneous bilateral intravitreal versus unilateral anti-vasculo-endothelial growth factors injection in an operating room setting. Pakistan J Med Sci 38(8):2324–2330
18. Lima LH, Zweifel SA, Engelbert M, Sorenson JA, Slakter JS, Cooney MJ et al (2009) Evaluation of safety for bilateral same-day intravitreal injections of anti-vascular endothelial growth factor therapy. Retina 29(9):1213–1217
19. Davis RP, Schefler AC, Murray TG (2010) Concomitant bilateral intravitreal anti-VEGF injections for the treatment of exudative age-related macular degeneration. Clin Ophthalmol 4:703–707
20. Cimbalas A, Svalbonaite E LG and AR (2012) Simultaneous and separate time bilateral intravitreal injection for patients with neovascular AMD and poor baseline visual acuity. Acta Ophthalmol, 250
21. Gregori NZ, Weiss MJ, Goldhardt R, Schiffman JC, Vega E, Mattis CA, et al. (2012) Randomized clinical trial of two anesthetic techniques for intravitreal injections: 4% liquid lidocaine on cotton swabs versus 3.5% lidocaine gel. Expert Opin Drug Deliv. 9(7):735–741
22. Shah M, Amoaku WMK. Same-day consecutive bilateral intravitreal injections of ranibizumab for the treatment of bilateral active choroidal neovascularization in age-related macular degeneration, vol 90. Acta Ophthalmol. England, p e491–e493
23. Abu-Yaghi NE, Shokry AN, Abu-Sbeit RH (2014) Bilateral same-session intravitreal injections of anti-vascular endothelial growth factors. Int J Ophthalmol 7(6):1017–1021
24. Chao DL, Gregori NZ, Khandji J, Goldhardt R (2014) Safety of bilateral intravitreal injections delivered in a teaching institution, vol 11, Expert opinion on drug delivery. England. pp 991–993.
25. Giocanti-Auregan A, Tadayoni R, Grenet T, Fajnkuchen F, Nghiem-Buffet S, Delahaye-Mazza C et al (2016) Estimation of the need for bilateral intravitreal anti-VEGF injections in clinical practice. BMC Ophthalmol 16:142
26. Fileta JB, Scott IU, Flynn HWJ (2014) Meta-analysis of infectious endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmic Surg Lasers Imaging Retina 45(2):143–149
27. McCannel CA (2011) Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: causative organisms and possible prevention strategies. Retina 31(4):654–661
28. Sachdeva MM, Moshiri A, Leder HA, Scott AW (2016) Endophthalmitis following intravitreal injection of anti-VEGF agents: long-term outcomes and the identification of unusual micro-organisms. J Ophthalmic Inflamm Infect 6(1):2
29. Green-Simms AE, Ekdawi NS, Bakri SJ (2011) Survey of intravitreal injection techniques among retinal specialists in the United States. Am J Ophthalmol 151(2):329–332
30. Chaturvedi R, Wannamaker KW, Riviere PJ, Khanani AM, Wykoff CC, Chao DL (2019) Real-world trends in intravitreal injection practices among american retina specialists. Ophthalmol Retin 3(8):656–662
31. Lau PE, Jenkins KS, Layton CJ (2018) Current Evidence for the Prevention of Endophthalmitis in Anti-VEGF Intravitreal Injections. J Ophthalmol 2018:8567912
32. Falavarjani KG, Nguyen QD (2013) Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye (Lond) 27(7):787–794
33. Freund KB, Vance SK (2011) Systemic safety of bilateral intravitreal anti-vascular endothelial growth factor injections, vol 31, Retina (Philadelphia, Pa.). United States, pp 1–3