The effects of prefilled syringe technology and masking on endophthalmitis risk following intravitreal injection of anti-vascular endothelial growth factor agents

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Abstract

Purpose

To evaluate the effect of prefilled syringe technology and different masking protocols on endophthalmitis rates following intravitreal injection (IVI).

Methods

Endophthalmitis cases following IVI between 3/1/2015 and 10/31/2022 at a single institution were reviewed. Three different periods of masking protocols were evaluated: no masking (5.1 years), universal masking (2.2 years), physician masking with optional patient masking (0.5 years).

Results

A total of 63 cases of endophthalmitis occurred following 248,879 IVI's (92,463 bevacizumab, 12,395 ranibizumab, 144,021 aflibercept), of which 177,129 used prefilled syringe technology. The use of prefilled syringes was associated with a significant decreased risk of endophthalmitis (odds ratio 0.25, 95% CI 0.15-0.42, $p<0.0001$). In multivariable analysis, different masking protocols had no effect on endophthalmitis risk ($p=0.974$). However, in culture-positive endophthalmitis cases, the use of face masks among all individuals ($p=0.011$) and physicians only ($p=0.019$) was associated with lower rates of endophthalmitis.

Conclusion

The use of prefilled syringes of anti-vascular endothelial growth factor agents was associated with a significant decreased risk of endophthalmitis following IVI. Masking protocols had no effect on risk of infection overall although masking was associated with lower risk of culture-positive cases.

Introduction

Anti-vascular endothelial growth factor (VEGF) medications are used to treat a variety of eye conditions, including wet age-related macular degeneration, proliferative diabetic retinopathy, diabetic macular edema, and retinal vein occlusion.[1] Despite their effectiveness, intravitreal injections are not without risks, and endophthalmitis is one of the most serious complications associated with the procedure.[2] Acute bacterial endophthalmitis is a severe intraocular infection that can lead to vision loss or blindness.[3] The incidence of endophthalmitis after intravitreal injections has been reported to range from approximately 1 in 500 injections to 1 in 19,000 injections, with a commonly reported incidence rate of 1 in 2000 injections.[3,4] Given the high volume of intravitreal injections performed each year, even a low incidence of endophthalmitis can result in a significant number of cases. Prevention of endophthalmitis after intravitreal injection is a priority in ophthalmic practice. Strategies to reduce the risk of infection include optimizing injection technique, using appropriate antiseptics such as povidone iodine or aqueous chlorhexidine, and implementing infection control measures in the clinical setting.[3,5,6,7]

In recent years, the use of prefilled syringe technology has become prevalent as it provides a number of advantages. Prefilled syringes offer consistent and accurate dosing, reducing the variability that may occur with manual preparation.[8,9] They save time in the clinic by reducing the time required for medication preparation, making the injection process more efficient.[8,9] They may reduce the risk of contamination, as the medication is contained in a closed system, minimizing the potential for contaminants to enter the syringe, which may reduce the risk of endophthalmitis .[8,9,10,11]

Another widespread infection control method that has been employed in clinical practice in recent years is the use of face masking. Recent studies have produced mixed results, showing

that face masks may produce the same result as a “no talking” policy, may increase the rate of endophthalmitis, or may not alter rates.[11,12,13,14] Our current study investigates the effect of prefilled syringe use and masking protocols on infection rates.

Methods

This single center retrospective cohort study was conducted at Austin Retina Associates in Austin, Texas and was approved by an independent Institutional Review Board (IRB). Cases of endophthalmitis following intravitreal injection were identified using billing records. Further information was collected on each post-IVI endophthalmitis case from clinical records, including type of medication administered; prefilled syringe status; patient age and sex; date of causative infection; date of presumed infection onset; microbial culture results; and visual acuity (VA) at baseline, presentation, 6 months and 12 months post-IVI. All data was de-identified and uploaded in a secure database.

All cases of presumed endophthalmitis following injection of bevacizumab, ranibizumab, and aflibercept between March 1, 2015 and October 31, 2022 were included in this study. Cases following IVI of other agents were excluded. All injections of bevacizumab were administered in prefilled syringes from a compounding pharmacy. Injections of ranibizumab and aflibercept were administered from conventional vials, in which the medication had to be transferred to a syringe, or from prefilled syringes from the manufacturer.

Masking Protocols

Different masking protocols were in place during three time periods. In time period 1 (March 1, 2015 to March 18, 2020), physicians/ancillary staff and patients were unmasked. In time period 2 (March 19, 2020 to May 13, 2022), physicians/ancillary staff and patients were all

required to wear masks as mandated by clinic guidelines. In time period 3 (May 14th, 2022, to October 31, 2022), only physicians and ancillary staff were required to mask while no mask mandate was in place for patients, although some patients chose to mask. During masking mandates, physicians, staff and patients were allowed to wear masks of their choosing, ranging from cloth masks to N95 masks. When patients wore masks, masks were taped during the intravitreal injection procedure based on physician preference.

Intravitreal Injection Protocol

All injections were performed in an office setting. Eyes were prepped with topical anesthetic and topical 5% povidone-iodine in a standard fashion. Injections were performed with a 30 or 31-gauge needle 3.5 to 4.0mm from the limbus. Subconjunctival lidocaine use, lid speculum use, conjunctival displacement prior to injection, and quadrant of injection were based on surgeon preference.

Endophthalmitis Treatment Protocol

All presumed cases of endophthalmitis were treated with a diagnostic vitreous or anterior chamber tap followed by injection of intravitreal antibiotics (vancomycin 1mg/0.1mL and ceftazidime 2mg/0.1ml). Based on physician preference, some cases were subsequently treated with pars plana vitrectomy. Topical antibiotics, steroids, and cycloplegics were prescribed based on physician preference.

Statistical Analysis

We conducted a Poisson regression analysis sing RStudio version 2021.09.1+372 to investigate the data, utilizing the count of endophthalmitis cases as the dependent variable, and considering factors such as the medication injected (conventional aflibercept, prefilled aflibercept, prefilled bevacizumab, conventional 0.5mg ranibizumab, prefilled 0.5mg

ranibizumab) and the use of face masks (masked, unmasked, only physicians masked) as independent variables. The cases were categorized into presumed endophthalmitis, culture-positive endophthalmitis, and oral flora-positive.

Results

Endophthalmitis Rates

A total of 63 cases of endophthalmitis occurred following 248,878 IVI's (92,463 bevacizumab, 12,395 ranibizumab, 144,020 aflibercept) over the course of 7.5 years, giving an overall infection rate of 0.025% or 1 in 3,950 injections. Prefilled syringe technology was used in 97.5% of ranibizumab injections (12,087 IVIs), 50.4% of aflibercept injections (72,579 IVIs), and all bevacizumab injections (92,463 IVIs). The rate of presumed endophthalmitis following conventional injection was 0.047% (1 in 2,110 injections) compared to 0.016% for prefilled syringes (1 in 6,107 injections, $p<0.0001$). The use of prefilled syringe technology was associated with a significantly decreased risk of presumed endophthalmitis compared to conventional vials (odds ratio 0.25, 95% CI 0.15-0.42, $p<0.0001$).

A total of 11 cases of culture-positive endophthalmitis occurred. The rate of culture-positive endophthalmitis following conventional vial injection was 0.006% (1 in 17,937 injections) compared to 0.004% for prefilled syringes (1 in 25,304 injections, $p=0.58$). A total of 4 cases of oral flora endophthalmitis cases occurred. The rate of oral flora positive endophthalmitis following conventional vial injection was 0.0013% (1 in 71,750 injections) compared to 0.0017% for prefilled syringes (1 in 59,043 injections, $p=0.87$)

In the first injection period (3/1/2015 to 3/18/2020), 134,097 total injections were administered and the rate of presumed endophthalmitis following conventional vial injection was 0.042% (1 in 2,363 injections) compared to 0.022% for prefilled syringes (1 in 4,393 injections,

p=0.04). In the second injection period (3/19/2020 to 5/13/2022), 91,402 total injections were administered and the rate of presumed endophthalmitis following conventional vial injection was 0.09% (1 in 1,094 injections) compared to 0.01% for prefilled syringes (1 in 9,426 injections, p<0.0001). In the third injection period (5/14/2022 to 10/31/2022), 23,380 total injections were administered and the rate of presumed endophthalmitis following conventional vial injection was 0.07% (1 in 1,379 injections) compared to 0.018% for prefilled syringes (1 in 5,500 injections, p=0.18).

We evaluated rates of endophthalmitis by medication and prefilled status. For conventional syringes, the rates of presumed and culture-positive endophthalmitis were 0.32% (1 in 308 injections) and 0% (no culture-positive cases) for ranibizumab and 0.046% (1 in 2,164 injections) (p=0.99 vs ranibizumab) and 0.006% (1 in 17,860 injections) for aflibercept (p=0.98 vs ranibizumab). The rates of presumed and culture-positive endophthalmitis were 0.019% (1 in 5137 injections) and 0.004% (1 in 23,115 injections) for prefilled bevacizumab. Rates of presumed and culture-positive endophthalmitis were 0.016% (1 in 6,043 injections, p=0.58 vs. bevacizumab) and 0.008% (1 in 12,087 injections, p=0.91 vs. bevacizumab) for prefilled ranibizumab and 0.012% (1 in 8,064 injections, p=0.0071 vs. bevacizumab) and 0.002% (1 in 36,289 injections, p=0.20 vs. bevacizumab) for prefilled aflibercept.

Multivariable Analysis

In multivariable analysis of presumed endophthalmitis cases controlling for prefilled syringe status and masking, the use of prefilled aflibercept (p=0.0037) and prefilled bevacizumab (p=0.0036) were associated with a decreased risk of infection. The use of face masks did not impact rates of presumed endophthalmitis (p=0.974).

In the context of culture-positive endophthalmitis cases, prefilled aflibercept was associated with a lower rate of infection (p=0.022). Additionally, the use of face masks among all individuals (p=0.011) and physicians only (p=0.019) was associated with significantly lower rates of culture-positive endophthalmitis (Table 1).

For oral-associated endophthalmitis cases (total of 4 cases), no factors, including the use of prefilled syringes or the use of face masks, were associated with reduced risk of infection.

Visual Outcomes

The overall average visual acuity at baseline, measured at the time of injection prior to endophthalmitis, was logMAR 0.71 (approximately 20/100 Snellen equivalent). The overall average visual acuity at 6 months post-endophthalmitis was logMAR 0.99 (~20/200 Snellen). At 12 months post-endophthalmitis, the overall average visual acuity was logMAR 0.91 (~20/160 Snellen). At 12 months post-infection, 57% of patients returned to within 2 lines of baseline visual acuity. Visual outcomes at 6 months and 12 months did not differ significantly between conventional and prefilled syringe cases overall (p=0.22) but did differ between injected medications (p=0.042).

In the conventional syringe cohort (table 2), average visual acuity at the time of endophthalmitis presentation was 1.61 logMAR (~20/800) improving to 0.92 logMAR (~20/160) at 6 months and 0.81 logMAR (~20/125) at 12 months. In the prefilled syringes cohort (table 3), visual acuity at time of endophthalmitis presentation was 1.93 logMAR (~20/800) improving to 1.42 logMAR (~20/500) at 6 months and 1.32 logMAR (~20/400) at 12 months, which were not significantly different than the conventional syringe cohort (p=0.36 at baseline, p=0.23 at 6 months, p=0.43 at 12 months).

In culture-positive endophthalmitis cases, visual acuity at the time of endophthalmitis presentation was 2.07 logMAR. In culture-negative endophthalmitis cases, visual acuity at the time of endophthalmitis presentation was 1.61 logMAR, a difference that was not statistically significant (p=0.09). At 6 months post-infection, visual acuity improved to 1.15 logMAR in the culture positive cases and 1.10 logMAR in the culture negative cases (p=0.87). At 12 months post-infection, visual acuity improved to 1.05 logMAR in the culture positive cases and 0.89 in the culture negative cases (p=0.62).

In oral flora positive cases, visual acuity at the time of endophthalmitis presentation was 2.5 logMAR and in non-oral flora culture positive cases visual acuity at the time of endophthalmitis presentation was 2.04 logMAR (p=0.23). At 6 months post-infection, visual acuity improved to 1.68 logMAR in the oral flora positive cases and 0.75 logMAR in the non-oral flora culture positive cases (p=0.18). At 12 months post-infection, visual acuity improved to 1.60 logMAR in the oral flora positive cases and 0.62 logMAR in the non-oral flora culture positive cases (p=0.12).

With regards to masking, visual acuity at the time of endophthalmitis presentation was 1.56 logMAR in period 1 (patients and physicians unmasked), 1.91 logMAR in period 2 (patients and physicians masked), and 2.18 logMAR in period 3 (only physicians masked). These results were not statistically significant (p=0.14). At 6 months post-infection, visual acuity improved to 0.87 logMAR in period 1, 1.26 logMAR in period 2, and 1.06 logMAR in period 3 (p=0.36). At 12 months post-infection, visual acuity improved to 0.81 logMAR in period 1, 1.21 logMAR in period 2, and 0.58 logMAR in period 3 (p=0.32).

Discussion

While rates of endophthalmitis following IVI of anti-VEGF agents remain relatively low, consequences of the infection can be devastating, leading to severe vision loss and blindness.[15] As intravitreal anti-VEGF therapy has become the mainstay of treatment for many common retinal vascular diseases, identifying risk factors, particularly those that may be modifiable, are of great importance.

In a single institution study including nearly 250,000 injections, we found that prefilled syringe technology was associated with a significant decreased risk of presumed endophthalmitis. Rates of presumed endophthalmitis were approximately 1 in 1,900 for conventional vials compared to 1 in 7,700 injections for prefilled syringes. In multivariable analysis, prefilled aflibercept and prefilled bevacizumab were both associated with decreased risk of presumed endophthalmitis. For culture-positive cases, prefilled aflibercept was associated with a decreased risk of infection.

In univariable analysis, when rates of infection were compared across medication types, we found that prefilled bevacizumab was associated with lower rates of presumed endophthalmitis compared to prefilled aflibercept although no difference was found in culture-positive cases. Previous studies have generally found no difference in endophthalmitis rates between medications.[4,17] It is unclear if non-infectious inflammation following aflibercept injection, or other possible causes, could account for the difference found in the current study, although both prefilled aflibercept and prefilled bevacizumab were independently associated with lower rates of presumed infection in multivariable analysis.

Multiple studies have examined endophthalmitis caused by common oral flora, such as streptococcus species, during IVI procedures.[16,17] Oral associated flora are of particular importance as infections with those organisms are often associated with worse visual

outcomes.[18,19] Previous studies have shown that a strict “no-talking” policy during IVI decreased rates of oral flora endophthalmitis presumably due to decreased opportunity for bacterial spread.[5,20] While the current study did not find any factors associated with the risk of oral-associated flora, the number of cases (4) was low, which may limit our ability for subgroup analysis.

Masking has the potential to decrease the risk of infection. However, past results have shown mixed effects on whether masking reduces the rates of endophthalmitis after IVI.[11,14,21] Masking has been proposed as a means of decreasing oral bacteria dispersion but may also increase air flow on the eyes if loose-fitting.[21] In our study we found that masking did not have a significant effect on the rate of presumed endophthalmitis cases but was associated with a significantly decreased risk of culture-positive cases during the time periods when all individuals and physicians were required to mask, indicating that there may be a protective effect from masking in some instances. It should be noted, however, that not all physicians within the study previously incorporated a strict no-talking policy. The use of masks by patients and physicians may accomplish a similar risk reduction as a no-talking policy.

In terms of visual outcomes, 57% of patients returned within 2 lines of baseline acuity by 12 months follow up. We found no difference in visual outcomes with the use of prefilled syringes or masking. Some studies have found that culture-positive and oral-associated endophthalmitis cases may result in worse visual outcomes.[22] In this study, we found no difference in visual outcomes, although the number of culture-positive cases was low, which may have limited our analysis.

This study has limitations, including its retrospective nature with various injection methods used between physicians. There was no standardization of face masks used by

physicians or patients, which could affect bacterial dispersion as poorly fitting masks could affect infection risk.[21] Further, physicians and patients may not have been completely adherent to masking protocols at all times, or physicians and patients may have opted to mask at a time when there was no masking protocol in place, leading to further possible variations in data. The number of culture-positive cases was relatively low, which may limit subgroup analysis. It is important to note that while all medications may use pre-filled syringe technology, bevacizumab is produced by local compounding pharmacies rather than at a central location through the manufacturer as aflibercept and ranibizumab are. Given that the primary variable for analysis was whether the injection was prefilled, bevacizumab injections were included in the prefilled injections category.

Our results support prior research demonstrating lower rates of post-IVI endophthalmitis with the use of prefilled syringes compared to conventional vials of medication. We obtained similar results when controlling for different masking protocols across time periods, finding that masking did not affect infection rates. As new medications come to market, prefilled syringe technology should be adopted as rapidly as can be safely achieved.

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Table 1: Multivariable analysis of endophthalmitis cases

	Presumed endophthalmitis cases		**Culture-positive cases**		**Oral-flora cases**	
Coefficients	**Estimate**	**Pr(>|z|)**	**Estimate**	**Pr(>|z|)**	**Estimate**	**Pr(>|z|)**
Intercept	-7.688	< 2e-16 *	-10.343	<2e-16 *	-11.182	<2e-16 *
Aflibercept prefilled	-1.388	0.00370 *	-2.175	0.0217 *	-0.013	0.994
Bevacizumab prefilled	-0.882	0.00359 *	-0.853	0.2496	-0.259	0.857
Ranibizumab 0.5 conventional	1.955	0.05413	-13.169	0.9970	-13.077	0.998
Ranibizumab 0.5 prefilled	-1.066	0.15406	-0.657	0.5723	1.770	0.251
Physicians and patients masked	0.012	0.97359	1.972	0.0113 *	0.240	0.853
Physicians masked	0.314	0.54985	2.295	0.0190 *	-16.759	0.997

*Indicates statistically significant

Table 2: Endophthalmitis cases following intravitreal injection with conventional syringes

Patient	Medication	VA at Injection	VA at 6 Months Post Endophthalmitis	VA at 12 Months Post Endophthalmitis	VA at Final Follow-up	Culture Results
1	Aflibercept	20/50	20/70	20/70	20/100	Negative
2	Aflibercept	20/50	20/400	20/200	20/100	Negative
3	Aflibercept	20/20	20/60	20/40	20/25	Negative
4	Aflibercept	CF	CF	CF	CF	Negative
5	Aflibercept	20/200	20/400	20/200	CF	Negative
6	Aflibercept	20/200	20/70	20/200	20/60	Negative
7	Aflibercept	20/60	CF	20/70	CF	Negative
8	Aflibercept	20/400	20/25	20/25	20/30	Negative
9	Aflibercept	CF	CF	20/400	20/400	Negative
10	Aflibercept	20/50	20/50	20/40	20/50	Negative
11	Aflibercept	20/20	20/30	20/30	20/30	*Coagulase Negative Staphylococcus*
13	Aflibercept	20/40	20/50	20/50	20/30	Negative
14	Aflibercept	20/50	20/70	20/70	20/60	Negative

15	Aflibercept	20/60	20/20	20/20	20/30	Negative
16	Aflibercept	20/20	20/25	20/30	20/30	Negative
17	Aflibercept	20/20	20/20	20/25	20/30	Negative
18	Aflibercept	20/40	20/50	20/40	20/30	Negative
19	Aflibercept	20/25	20/30	20/30	20/30	Negative
20	Aflibercept	CF	CF	CF	CF	Negative
21	Aflibercept	20/50	CF	CF	CF	Negative
22	Aflibercept	20/80	20/200	CF	CF	Negative
23	Aflibercept	20/30	20/40	20/30	20/30	Negative
24	Aflibercept	CF	CF	LP	LP	Negative
25	Aflibercept	CF	CF	CF	CF	Negative
26	Aflibercept	20/30	20/50	20/40	20/30	Negative
27	Aflibercept	20/25	20/50	20/40	20/40	Negative
28	Aflibercept	20/40	20/30	20/25	20/25	Negative
29	Aflibercept	20/30	20/70	20/70	20/50	Negative
30	Aflibercept	20/80	20/100	20/100	20/150	Negative

31	Aflibercept	20/25	20/30	20/40	20/20	*Staphylococcus epidermis*
32	Aflibercept	20/25	20/40	20/40	20/40	Negative

VA = visual acuity

Table 3: Endophthalmitis cases following intravitreal injection with prefilled syringes

Patient	Medication	VA at Injection	VA at 3 Months Post Endophthalmitis	VA at 6 Months Post Endophthalmitis	VA at 12 Months Post Endophthalmitis	VA at Final Follow-up	Culture Results
1	Bevacizumab	HM	20/40	20/30	20/30	20/30	Negative
2	Bevacizumab	20/25	20/20	20/25	20/25	20/25	Negative

3	Bevacizumab	20/30	20/50	20/40	20/25	20/20	Negative
4	Bevacizumab	HM	20/100	20/200	20/60	LP	Negative
5	Bevacizumab	20/30	20/60	20/60	20/60	20/20	Negative
6	Bevacizumab	20/40	20/200	20/150	20/60	20/40	Negative
7	Bevacizumab	CF	CF	CF	CF	CF	Negative
8	Bevacizumab	20/40	20/20	20/20	20/20	20/20	Negative
9	Bevacizumab	20/25	CF	CF	20/200	CF	*Coagulase Negative Staphylococcus*
10	Bevacizumab	CF	n/a	n/a	n/a	HM	Negative
11	Bevacizumab	20/20	20/60	n/a	n/a	20/60	Negative

12	Bevacizumab	20/60	20/100	20/60	20/150	20/150	Negative
13	Aflibercept	20/60	20/50	20/125	20/80	20/70	Negative
14	Aflibercept	20/30	20/30	20/40	20/40	20/30	*Granulicatella adiacens*
15	Aflibercept	20/25	20/200	20/200	20/100	CF	Negative
16	Aflibercept	20/80	20/60	20/60	20/60	20/100	Negative
17	Aflibercept	20/150	20/400	20/150	20/400	HM	Negative
18	Aflibercept	20/150	20/400	20/150	20/400	HM	*Coagulase Negative Staphylococcus*
19	Aflibercept	CF	CF	CF	CF	CF	Negative
20	Aflibercept	CF	CF	CF	CF	CF	Negative
21	Aflibercept	20/25	20/25	20/20	20/25	20/25	Negative
22	Aflibercept	20/40	20/50	20/50	20/40	20/40	Negative
23	Aflibercept	CF	NLP	NLP	NLP	NLP	Negative