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Original Research Article

Frequency of endophthalmitis following intravitreal bevacizumab injection using povidone-iodine vs povidone-iodine with topical antibiotics as prophylaxis in patients of macular oedema

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Abstract: *This study compared povidone-iodine alone versus povidone-iodine with antibiotics to prevent endophthalmitis after intravitreal bevacizumab injections for macular oedema. It aimed to find the best infection prevention method.* ***Objective:*** *To determine the efficacy of per-operative 5% povidone-iodine alone vs combined per-operative 5% povidone-iodine with topical antibiotics for reducing the frequency of endophthalmitis in patients undergoing repeated intravitreal injection of Anti-VEGF (Bevacizumab).* ***Methods:*** *This randomised control trial was conducted at the Department of Ophthalmology, Sir Ganga Ram Hospital, Lahore. Patients meeting inclusion criteria were enrolled after taking informed written consents, and two equal groups were made on a random basis using a lottery method: Group A (Povidone Iodine Alone) and Group B (Povidone Iodine with Topical Antibiotics). The procedure was performed per the hospital's standard protocol, and variables were noted for data analysis.* ***Results:*** *The mean age was 51.23±12.43 years, with a balanced gender ratio (52.6% male, 47.4% female). Injections were predominantly in the right eye (52.9%) versus the left (47.1%). Diabetic macular oedema (57.4%) was most prevalent, followed by choroidal neovascularization (17.1%), central retinal vein occlusion (8.9%), branch retinal vein occlusion (10.9%), and other pathologies (5.7%). Groups A and B had similar baseline characteristics ($p>0.05$). Both groups had a 0.6% endophthalmitis rate ($p=1.000$), each with 175 patients.* ***Conclusion:*** *This study comparing 5% povidone-iodine alone versus 5% povidone-iodine with topical antibiotics for prophylaxis during intravitreal bevacizumab injections did not demonstrate a significant difference in the incidence of endophthalmitis between the two groups.*

Keywords: Endophthalmitis, Intravitreal Bevacizumab, Povidone Iodine

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Introduction

The normal ocular flora comprises bacteria that typically do not cause ocular infections under normal conditions but can lead to infections following ocular surgery, trauma, or in immunocompromised patients (1). The range of these microorganisms varies with age and geographical distribution. Therefore, ophthalmologists must understand the normal ocular flora before prescribing prophylactic antibiotics and treating infections (2).

Anti-VEGFs (Anti-Vascular Endothelial Growth Factors) in the form of intravitreal injections have revolutionised the management of posterior segment pathologies such as age-related macular degeneration, diabetic retinopathy, and retinal vascular occlusion, providing both functional and anatomical improvement (3, 4). Repeated injections are often necessary for patients undergoing anti-VEGF therapy for retinal diseases (5). Intravitreal injections, while effective, carry risks such as endophthalmitis, a severe intraocular inflammation from bacterial or fungal infection. Symptoms include red eye, pain, decreased vision, and inflammation (6).

Bevacizumab, ranibizumab, and aflibercept are commonly used anti-VEGF agents for inhibiting VEGF-A and reducing neo-vessel formation and macular oedema. Anti-VEGF therapy usually begins with monthly injections, followed by a tailored protocol over several months or years (7). Bevacizumab (Avastin) is an FDA-approved monoclonal antibody used intravenously for certain cancers and retinal pathologies (8). In contrast, ranibizumab (Lucentis) is an antibody fragment (fab) designed explicitly for intraocular use and is more petite than bevacizumab. Ranibizumab received FDA approval in 2006 for treating wet age-related macular degeneration (AMD) (5). Another FDA-approved intraocular anti-VEGF medication is aflibercept (Eylea), an artificial protein containing VEGF receptors that neutralise VEGF by binding and sequestering it. Due to this mechanism, aflibercept is also known as "VEGF Trap-Eye" (4,9).

The incidence of endophthalmitis after anti-VEGF injections is low (0.02-0.08%) but increases with repeated injections (6). Topical antibiotics have been used for prophylaxis, but studies have shown little benefit (3). Overuse of antibiotics can create resistant strains, increase drug costs, and lead to adverse reactions (10). Current evidence suggests that per-operative 5% topical povidone-iodine (PI) is the most effective prophylaxis in reducing post-injection bacterial infection (7).

A retrospective study conducted at the B.P. Koirala Lions Centre for Ophthalmic Studies in 2018 examined the outcome of intravitreal bevacizumab injections without pre- and postoperative antibiotics over two years. Among 503 eyes analysed, the incidence of endophthalmitis was only 0.0019%, significantly lower than rates reported in other studies. The findings suggest that intravitreal injections can be safely administered without preoperative or postoperative antibiotics (1).

Another retrospective case-control study conducted at the Department of Ophthalmology, Centro Hospitalar Universitário de São João, Porto, Portugal, 2018 compared the incidence of endophthalmitis after intravitreal injection with and without topical antibiotic prophylaxis. Among 33,515 injections, 13 cases of endophthalmitis were identified, with a similar incidence rate in both groups. Five cases of endophthalmitis were reported out of 14,828 intravitreal injections with topical antibiotic prophylaxis (0.0337%). In contrast, eight cases of endophthalmitis were identified out of 18,687 intravitreal injections without topical antibiotic prophylaxis (0.0428%). Thus, the use of topical antibiotics did not significantly affect the occurrence of endophthalmitis (11).

Topical antibiotics after intravitreal Anti-VEGF have been used for prophylaxis, but studies have shown little benefit. The overuse of antibiotics could create and proliferate resistant strains, escalating drug costs and increasing the likelihood of adverse reactions to the drugs administered.

Methodology

This randomised control trial was conducted at the Department of Ophthalmology, Sir Ganga Ram Hospital, Lahore, for 6 months after the approval of the synopsis. A sample size of 350 patients was calculated. Inclusion criteria were patients with macular oedema, age range from 20-70 years, genders, no anterior chamber reaction, no vitreous activity and transparent cornea. However, patients with anterior chamber reaction, corneal opacity, any ocular infection, vitreous haemorrhage, vitreous activity, and dense cataract that obscures the view of the posterior segment assessing vitreous activity were excluded. Patients with macular oedema due to various retinal pathologies, documented clinically and diagnostically using Zeiss Cirrus Photo 600 OCT, requiring Intravitreal Bevacizumab, were included in the study after obtaining approval from the ethical review board of the hospital. Patients were counselled and guided about the survey, and consent was obtained. The patients were divided into two groups (175 eyes in each group) using random allocation software 2.0 to create a randomisation sequence using the random allocation method. Consort 2010 flow diagram for randomised controlled trial was used. In Group A (175 patients), after the topical application of 1% proparacaine, 5% PI for 5 minutes was used to disinfect eyebrows, eyelids, periorbital skin and eyelashes. A sterile eye was draped, and an eye speculum was applied. A 5% povidone-iodine solution was instilled conjunctivally for 3 minutes, followed by irrigation. Using a 30-gauge insulin syringe, a freshly prepared, prefilled, sealed Bevacizumab (Avastin) injection was administered into the mid-vitreous cavity through the superotemporal quadrant, 3.5mm from the limbus in pseudophakic eyes and 4mm in phakic eyes, under an operating microscope in the eye surgery theatre. Post-injection, 5% PI was applied to the injection site, and an eye pad was placed for 4 hours. Patients were discharged after the procedure. Follow-ups were done on the first and seventh post-injection day using the following clinical examination parameters: redness of the eyes, ocular pain, decreased vision, lid oedema, and anterior chamber and vitreous activity. In group B (175 patients), the same procedure was done as in group A; in addition, post-injection topical antibiotic (fluoroquinolone 0.3%) was advised four times a day for seven days. The follow-up protocol was the same as in group A. The injection was performed in the eye operation theatre by a Principal researcher, following a specific protocol. The role of the Principal researcher was to guide and counsel the patients, obtain consent, collect pre-injection data, perform intravitreal Bevacizumab injection, and do follow-ups with data collection. Data was analysed using SPSS 25.0.

Results

In this study involving 350 participants, the mean age was 51.23±12.43 years. The participants were categorised into two age groups: 20-50 (44.3%) and 51-70 (55.7%). Gender distribution among the participants was relatively balanced, with 52.6% male and 47.4% female. Regarding the eye side, 52.9% of participants received injections in the right eye (OD), while 47.1% received injections in the left eye (OS). The most common retinal pathology among the participants was diabetic macular oedema (DME), accounting for 57.4% of cases. Other retinal pathologies included choroidal neovascularisation (CNV) in 17.1% of cases, central retinal vein occlusion (CRVO) in 8.9% of cases, branch retinal vein occlusion (BRVO) in 10.9% of cases, and other miscellaneous pathologies in 5.7% of cases, as given in Table 1.0 below.

Both Group A (5% povidone-iodine alone) and Group B (5% povidone-iodine with topical antibiotics) demonstrated statistically similar baseline characteristics, as evidenced by a p-value greater than 0.05 for all variables assessed, as given in Table 2.0. Group mean values were compared using measures of central tendency (mean) and variability (standard deviation), and a t-test was used. Frequency distributions across groups were analysed using the chi-square test. A significance level of $p \leq 0.05$ was used to determine statistically significant results.

The incidence of endophthalmitis following intravitreal bevacizumab injections was evaluated in two groups: Group A (5% povidone-iodine alone) and Group B (5% povidone-iodine with topical antibiotics), each consisting of 175 patients. The endophthalmitis rates were identical in both groups, with only one patient (0.6%) affected. This finding suggests no statistically significant difference in the incidence of endophthalmitis between the two prophylactic regimens (p-value = 1.000), as given in Table 3.0.

Table 1 Baseline Characteristics of the Study Sample

Characteristics	Participants n=350
Age (20-70years)	51.23±12.43
• 20-50 years	155 (44.3%)
• 51-70 years	195 (55.7%)
Gender	
• Male	184 (52.6%)
• Female	166 (47.4%)
Eye Side	
• OD	185 (52.9%)
• OS	165 (47.1%)
Retinal Pathology	
• DME	201 (57.4%)
• CNV	60 (17.1%)
• CRVO	31 (8.9%)
• BRVO	38 (10.9%)
• Others	20 (5.7%)

Table 2 Comparison of Baseline Characteristics between the Groups

Characteristics	Group A n=175	Group B n=175	p-value
Age (20-70years)	50.80±11.99	51.66±12.87	0.517
• 20-50 years	81 (46.3%)	74 (42.3%)	0.519
• 51-70 years	94 (53.7%)	101 (57.7%)	
Gender			
• Male	89 (50.9%)	95 (54.3%)	0.593
• Female	86 (49.1%)	80 (45.7%)	
Eye Side			
• OD	88 (50.3%)	97 (55.4%)	0.392
• OS	87 (49.7%)	78 (44.6%)	
Retinal Pathology			
• DME	103 (58.9%)	98 (56.0%)	0.563
• CNV	26 (14.9%)	34 (19.4%)	
• CRVO	16 (9.1%)	15 (8.6%)	
• BRVO	22 (12.6%)	16 (9.1%)	
• Others	8 (4.6%)	12 (6.9%)	

**Independent Sample t test, ** Chi Square test, taking p-value >0.05 as insignificant.*

Table 3 Comparison of Frequency of Endophthalmitis Characteristics between the Groups

Endophthalmitis	Group A (n=175)	Group B (n=175)	p-value
Yes	1 (0.6%)	1 (0.6%)	1.000
No	174 (99.4%)	174 (99.4%)	
Total	175 (100.0%)	175 (100.0%)	

Fisher's Exact Test, taking p-value >0.05 as insignificant.

Discussion

Macular oedema, characterised by fluid accumulation in the retina, often requires treatment with intravitreal injections like bevacizumab to manage vascular endothelial growth factor (VEGF) (12). However, these injections carry a risk of endophthalmitis, a potentially serious complication (13, 14). Due to limited data, a study was conducted where 350 patients with macular oedema were randomly divided into two equal groups of 175 patients each. This research compared the use of 5% povidone-iodine alone versus 5% povidone-iodine combined with topical antibiotics for prophylaxis during intravitreal bevacizumab injections, aiming to evaluate the effectiveness of these approaches in reducing the incidence of post-injection complications like endophthalmitis.

The mean age of the patients in this study was 51.23±12.43 years. Previously, almost a similar mean age of 50.38±5.20 years and 52.27±6.8 years was reported by Ali et al. (2018) and Javed et al. (2022) in Pakistan, respectively (15,16). However, some other studies reported higher mean age, which may be associated with their inclusion criteria. Mean age of 54.47±9.68 years was reported by Saigol et al. (2021) in Pakistan, 58 (range 22-78) years by Saeed et al. (2013) in Pakistan, 59.62 years (range 19-91) years by Shrestha et al. (2020) in Nepal and 79 (range 69-85) years by Bhatt et al. (2015) in India (17,18,1,19).

In this study, there were 52.6% males and 47.4% females. Previously, similar male dominance in the study cohort was reported by Ali et al. (2018) as 68.0%, by Javed et al. (2022) as 58.0% and by Saigol et al. (2021) as 56.0% (15, 16, 17). But some other studies reported inverse findings where male participants were 41.2% and 42.5% of the study sample, as reported by Bhatt et al. (2015) and Iqbal et al. (2019), respectively (19,20). Regarding the eye side, 52.9% of participants received injections in the right eye (OD), while 47.1% received injections in the left eye (OS). Shrestha et al. (2020) reported 52.5% right eye (OD) in their study sample (1).

The most common retinal pathology among the participants was diabetic macular oedema (DME), accounting for 57.4% of cases. Other retinal pathologies included choroidal neovascularisation (CNV) in 17.1% of cases, central retinal vein occlusion (CRVO) in 8.9% of cases, branch retinal vein occlusion (BRVO) in 10.9% of cases, and other miscellaneous pathologies in 5.7%. Almost similar findings were given by Saeed et al. (2023) as DME (55.8%), CNV (21.2%), CRVO (7.7%), BRVO (9.6%), Eales (3.8%) and others 1.9%. Both Group A (5% povidone-iodine alone) and Group B (5% povidone-iodine with topical antibiotics) demonstrated statistically similar baseline characteristics, as evidenced by a p-value greater than 0.05 for all variables assessed (18).

The incidence of endophthalmitis following intravitreal bevacizumab injections was evaluated in two groups: Group A (5% povidone-iodine alone) and Group B (5% povidone-iodine with topical antibiotics), each consisting of 175 patients. The endophthalmitis rates were identical in both groups, with only one patient (0.6%) affected. This finding suggests that there was no statistically significant difference in the incidence of endophthalmitis between the two prophylactic regimens (p-value = 1.000). Previously, a lower rate of endophthalmitis following intravitreal bevacizumab injections was reported by Saeed et al. (2013) as 0.03%, by Baudin et al. (2022) as 0.024% and by Shrestha et al. (0.0019%) (18, 21, 1). However, while comparing it between the two groups, Torres-Costa et al. (2021) reported it 0.03% vs 0.04%; p-value=0.675 and Bhatt et al. (2015) reported it 0.22% vs 0.20%; p-value=0.750, respectively between group A and group B (8, 19).

Conclusion

In conclusion, this study comparing 5% povidone-iodine alone versus 5% povidone-iodine with topical antibiotics for prophylaxis during intravitreal bevacizumab injections did not demonstrate a significant difference in the incidence of endophthalmitis between the two groups.

Both regimens showed similarly low rates of endophthalmitis occurrence. These findings suggest that either approach may be effective in preventing post-injection complications. Further research is warranted to explore other factors that may influence the risk of endophthalmitis in this context. The study's strength is its randomised design with balanced groups, which enhances comparability. Additionally, the study focused on a clinically relevant outcome- endophthalmitis incidence following intravitreal injections. Limitations include the relatively small number of endophthalmitis cases, limiting statistical power. The study may also not account for other factors influencing endophthalmitis risk. Further research with larger sample sizes and consideration of additional variables is needed for more comprehensive conclusions.

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Declarations

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All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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