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Original Article

Real-World Anti-VEGF Practices in Pakistan: A Nationwide Study of Ophthalmologists' Practice Patterns and Challenges

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ABSTRACT

Objective: To evaluate practice patterns and safety protocols related to intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections among ophthalmologists in Pakistan, and to assess the perceived clinical and economic impact of the ban on bevacizumab in Punjab province.

Study Design: Cross-sectional study.

Place and Duration of Study: Nationwide study conducted across Pakistan from Oct to Nov 2024.

Methodology: A structured 30-item questionnaire was distributed electronically to 160 ophthalmologists through Pakistan Vitreo-Retinal Society. Participation was voluntary and anonymous. Frequencies and percentages were calculated for different variables.

Results: A total of 100 ophthalmologists responded. Practice settings included private practice (52%), Trust-based facilities (40%), and government hospitals (8%). Bevacizumab was the most frequently used agent (68%), followed by aflibercept (29%) and ranibizumab (3%). Seventy-four percent of practitioners indicated that they employed multi dose vial practices for administering aflibercept and ranibizumab injections. For administering injections, 92% practitioners preferred topical anesthesia, 90% used conjunctival sac povidone iodine, while 90% prescribed post-injection topical antibiotics for a week. Seventy-six percent of ophthalmologists preferred to use pre-filled, sterilized, single dose of bevacizumab injection meeting FDA compounding standards. Special informed consent for off-label bevacizumab use was obtained by 48% of respondents. Following the bevacizumab ban in Punjab, 93% (53 out of 57) respondents reported shifting to alternative therapies while 82.5% (47 out of 57) perceived significantly worsening patient outcomes.

Conclusion: Significant variability exists regarding the intravitreal anti-VEGF practices in Pakistan. The bevacizumab ban had substantial perceived impact on treatment accessibility and affordability.

Keywords: Anti-VEGF Therapy, Avastin, Bevacizumab, Endophthalmitis, Intravitreal Injection.

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INTRODUCTION

Intravitreal injection (IVI) therapy is the mainstay in treatment of many visual disorders, such as age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vascular diseases.[1] Anti-VEGF drugs, in recent past, have gained significant attention because they suppress abnormal vascularization and reduce macular edema. Global demand for these therapies is growing, with increased use in North America, Europe and India.[2-4]

Anti-VEGF treatments like bevacizumab, ranibizumab, and aflibercept, have proven treatment efficacy.[5] Despite the positive outcomes, frequent, widespread application of IVI carries potential risks. The most serious complication is endophthalmitis, a severe infection caused by microbial contamination, with an occurrence rate of 0.019% per injection.[6] Click or tap here to enter text. This risk underscores the importance of strict safety protocols during IVI procedures. Studies have also observed that uniform aseptic techniques and standardized protocols significantly reduce the rate of complications following injections.[7]

Although anti-VEGF therapy has become the cornerstone in treating retinal diseases, there is insufficient data regarding practice patterns, safety procedures, and regulatory changes in Pakistan. The recent ban on bevacizumab has compounded these issues, affecting healthcare service delivery and adding significant financial burden for healthcare professionals and patients. Literature on the variability of clinical practices in a previous study was inconsistent.[8] Though regional guidelines, such as those published by Punjab Healthcare Commission, aim to standardize IVI practices to protect patients and

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minimize complications however, there is lack of comprehensive national level recommendations.[9]

This study aimed to explore the intravitreal anti-VEGF practice patterns among ophthalmologists in Pakistan regarding safety measures, consent protocols and adaptation to the recent ban of bevacizumab.

METHODOLOGY

This was a descriptive, cross-sectional study. The study was conducted nationwide across Pakistan, with the online survey remaining open for responses from October to November 2024. Institutional Ethical Review Committee approval was obtained prior to study commencement (Reference no. ERC30/AST2-24).

Inclusion Criteria: Active ophthalmologists of either gender and any group, who were members of the Pakistan Vitreo-Retinal Society (PVRS) were included.

Exclusion Criteria: Ophthalmologists not performing intravitreal anti-VEGF injections in Pakistan were excluded.

Given the exploratory nature of the study and the absence of prior similar data from Pakistan, a convenience sampling technique was employed. The sample consisted of ophthalmologists who were active members of the Pakistan Vitreo-Retinal Society (PVRS). A total of 100 complete responses were obtained, which was considered adequate for descriptive purposes based on the estimated active PVRS membership of approximately 160 ophthalmologists at the time of study.

An electronic questionnaire containing 30 items was developed using Google Forms. The instrument was designed by senior retina specialists following a review of published literature on anti-VEGF practices in low- and middle-income countries. Most questions were closed-ended, including both multiple-choice and single-choice formats. Clarity and comprehensiveness were established through pilot testing on five ophthalmologists before final distribution.

The questionnaire covered five thematic domains: (1) administration procedures (aseptic technique, anesthesia type, injection handling); (2) anti-VEGF agent procurement and preparation (aliquoting, cold chain maintenance, supply source); (3) consent practices, including off-label bevacizumab use; (4) systemic risk assessment and pre-injection medical screening; and (5) practice modifications following the bevacizumab ban in Punjab province.

An online invitation link was distributed via professional mailing lists and social media platforms with the assistance of the PVRS. Participation was voluntary, and all responses were collected anonymously to minimize social desirability bias. Each respondent was permitted only one submission to maintain data integrity. Respondents could review and edit their answers before final submission, after which no changes were permitted. No identifying information was recorded.

Data were exported to Microsoft Excel for cleaning and statistical processing. Only fully completed questionnaires were included in the final analysis. Since most variables were categorical, results were expressed as frequencies and percentages. Subgroup analyses were conducted to examine variations across institutional types (private, charitable/trust-based, and government facilities).

RESULTS

A total of 100 ophthalmologists who practice in Pakistan took part in the study. The majority were consultants (78%), followed by fellows (12%) and residents (10%). Most respondents (62%) had over 10 years of clinical experience, 23% had 5-10 years while 15% had less than 5 years' experience. Geographically, more than half (57%) of the participants practiced in Punjab, 21% in Sindh, 11% in Khyber Pakhtunkhwa, 7% in Islamabad Capital Territory, and 4% in Baluchistan. Institutional settings were diverse, over half (52%) in private practice, 40% in charitable/trust-based facilities, and 8% in government hospitals, indicating predominance of private and charitable institutions offering intravitreal injection (IVI) in Pakistan (see Table-I).

The frequency of IVIs administered varied: 38% reported performing 0–10 injections per week, 24% performed 11–30, 13% performed 31–50, 6% performed 51–100, while 19% performed more than 100 injections weekly, reflecting wide heterogeneity in procedural volumes across practices.

Regarding the pharmacological option, the most frequently used anti-VEGF drug nationwide was bevacizumab (68%), followed by aflibercept (29%) and then ranibizumab (3%).

The selection of injection settings varied substantially according to institutional arrangements. As shown in Figure-1, most facilities that were conducted in a private setting used main OR to inject. Still, the charitable/trust facilities mainly depended on

the clean designated rooms and main operating rooms. Government hospitals, in contrast, have documented limited application of varied settings, with most of the injection taking place in clean rooms.

Table-I: Demographic Characteristics of Respondents (n = 100)

Characteristic	n (%)
Level of Practice	
Consultant	78 (78)
Fellow	12 (12)
Resident	10 (10)
Experience	
>10 years	62 (62)
5–10 years	23 (23)
<5 years	15 (15)
Province	
Punjab	57 (57)
Sindh	21 (21)
KPK	11 (11)
ICT	7 (7)
Balochistan	4 (4)
Practice Setup	
Private	52 (52)
Charitable Trust	40 (40)
Government	8 (8)

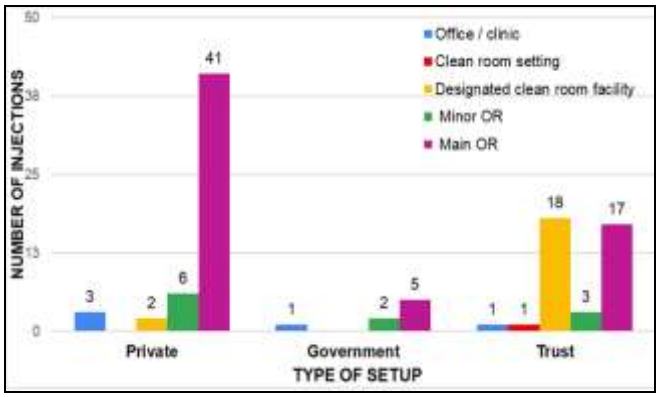

Figure-1: Intravitreal Injection Setting (office/clinic, clean room, designated clean room facility, minor operating room, and central operating room) distribution among Private, Government, and Trust Healthcare Setups in Pakistan

Consent processes were found to have variability. In aflibercept and ranibizumab, FDA/NICE-approved drugs, 73% of ophthalmologists gave standard written informed consent. However, with off-label usage of bevacizumab, 48% had special informed consent overtly recognizing that it was not licensed to be used intraocularly, whereas 52% had not. Such a disparity raises issues of ethical and medico-legal standards of clinical practice in the current context of the newly implemented national restrictions on the use of bevacizumab.

There was a significant variation in the practices used by ophthalmologists after injections. About 39% recommended eye patching immediately after the procedure, and 90% prescribed topical antibiotics up to one week after the injection while 10% also prescribe oral antibiotics for 5 days. The follow-up and review schedules were also heterogeneous; 30% of the respondents planned to have a follow-up one month, 27% did not specify a follow-up time, 22% reviewed patients immediately after the procedure and 20% reviewed at 1 week.

Table-II: Consent practices for Food and Drug Administration (FDA)/ National Institute for Health and Care Excellence (NICE) -approved and off-label anti-VEGF agents (n=100)

Consent type	Yes n(%)	No n(%)
Written consent for FDA/NICE-approved drugs	73 (73)	27 (27)
Special consent for (off-label use)	48 (48)	52 (52)

FDA: Food and Drug Administration; NICE: National Institute for Health and Care Excellence

Systemic risk factor evaluation preceding IVI was not performed consistently. Although a proportion (80%) conducted screening via history taking(blood glucose, cardiac assessment, stroke history, and pregnancy), 20 % never assessed systemic risk factors. 44% respondents don't consider blood glucose level before giving injection while 41 % and 14 % had a cut off limit of 200mg/dl and 300mg/dl respectively for random blood glucose level. Systemic assessment is heterogeneous which depicts the institutional disparity and the lack of national standards.

In our study, 68% of ophthalmologists nationwide reported routine use of bevacizumab as their primary anti-VEGF agent, followed by aflibercept at 29%, while ranibizumab was used by 3%. Additionally, 74% of practitioners indicated they also employed multi dose vial practices for administering these injections. The distribution of practices is summarized in Table-III.

Table-III: Baseline Primary anti-VEGF Agents used Nationwide (n=100)

Agent (before ban)	n (%)
Bevacizumab (primary agent)	68(68%)
Aflibercept	29(29%)
Ranibizumab	3(3%)
Reported use of multidose-vial practice for aflibercept and ranibizumab	74(74%)

In late 2023, the prohibition of intravitreal bevacizumab in Punjab led to notable shifts in practice patterns among ophthalmologists working in the province. After the provincial ban, 53 of 57

ophthalmologists (93%) said they switched to alternative therapies. Majority of the respondents from Punjab changed to aflibercept as their primary agent (78.9), whereas many used periocular or suprachoroidal triamcinolone acetonide injections as an adjunctive or alternative therapy. The number of respondents who did not change to another agent was four (7%) as given in Figure-2.

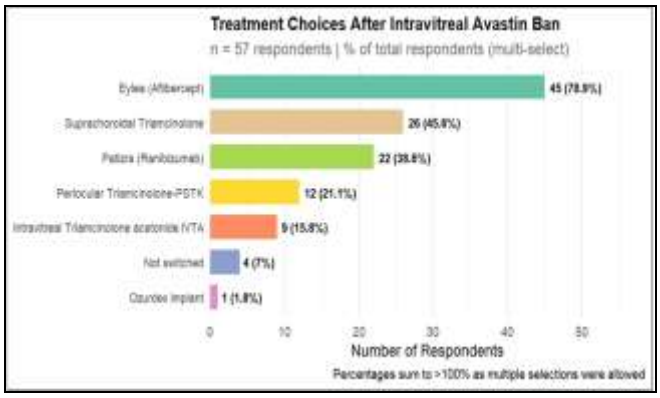

Figure-2: Frequency of Alternative Treatment Choices Following Provincial Ban on Intravitreal Bevacizumab

The ban has potentially significant negative impacts on patient outcomes. Most respondents (82.5%) said their patients were significantly worse after the ban, while 5.3% have mentioned no change.

Financially, two-thirds of respondent clinicians reported that their practices suffered severe financial loss, with others indicating no loss. This difference suggests that the type of institutions and socioeconomic status of patients could be the mediators of the economic impacts of the ban.

DISCUSSION

This nationwide study provides a comprehensive analysis of contemporary intravitreal anti-VEGF (vascular endothelial growth factor) practices among ophthalmologists in Pakistan, including the key areas of procurement, preparation, administration, patient consent and post-injection care. The results highlight the extensive usage of bevacizumab as the first line agent before its recent ban by the Punjab provincial government, with a shift to higher-costing agents. The findings indicate considerable heterogeneity in clinical practice which directly impacts patient safety and equitable access to sight-saving treatment.

Notably, the majority of respondents were experienced consultants (78%) primarily working in private or trust-based settings. The lower participation of residents (10%) indicates that, despite IVI being a straightforward procedure, its associated risks have led many institutions to entrust it to senior doctors.

Among the available anti-VEGF agents, Bevacizumab was the most commonly used (68%), despite being an off-label drug with a slightly higher risk of infective endophthalmitis. This increased risk is attributed to the practice of preparing multiple injections from a single vial.[10] The primary reason for its widespread use is its cost-effectiveness. At least 76% of ophthalmologists prefer a pre-filled, single-use, sterilized injection that meets FDA standards and maintains a well-regulated cold chain. This preference reflects a strong demand for safer, more convenient, and standardized administration methods. Recent studies also indicate that anti-VEGF medications provided in prefilled syringes may reduce the risk of contamination and injection-related complications while showing procedural efficiency due to which clinicians prefer prefilled syringes to vials.[11,12] There is also growing evidence that injection device technology impacts procedure safety. Gjølberg *et al*. demonstrated that special syringes designed without silicone oil lubricant not only improve patient safety profile but also maintain the functional integrity of compounded anti-VEGF agents for up to 30 days, as compared to standard lubricated syringes.[13]

Despite the widespread use of intra-vitreal injection techniques globally, standardized guidelines for their administration remain lacking. There is no clear consensus on the use of sterile drapes, speculums, masks, or pre- and post-operative antibiotics. Our findings reveal significant variability in pre-injection techniques within our region, consistent with previously reported observations.[8,14] In 2014, Avery *et al*. proposed a set of guidelines following a consensus among a panel of experts.[15] Agreed-upon recommendations included: (1) the use of povidone-iodine (5–10%) at the injection site, (2) the omission of pre-, peri-, and post-injection antibiotics, (3) the use of either sterile or non-sterile gloves, (4) no supporting evidence for the use of a sterile drape, and (5) the recommendation of surgical masks and monitoring intraocular pressure (IOP) before and after injection. However, no consensus was reached on (1) applying povidone-iodine to the eyelids and eyelashes, (2) the use of a speculum, and (3) the necessity of pupillary dilation. Our findings shows that majority of the respondents (90%) gave pre-injection antibiotics for at least one week while a minority (9%) only gave pre- injection topical

antibiotic at the time of injection and 10% give oral antibiotics as well for 5 days. This suggests a deviation from expert guidelines, as most ophthalmologists still use pre-injection antibiotics despite recommendations against them and also increases the risk for multidrug resistance.[16] Topical anesthesia was almost always utilized (92%), indicating a preference for patient comfort and doctor's confidence.

Furthermore, our findings show significant variability in the handling, preparation, and storage of Bevacizumab, raising concerns about sterility, dosing consistency, and infection risk. The challenges and adaptations observed in India, such as the lack of compounding pharmacies and limited affordability as compared to USA which has FDA approved 503b compounding facilities, provide a comparable perspective on the hurdles faced in Pakistan.[3,4] Most ophthalmologists (64%) prepare aliquots on-site, but practices like multiple punctures without disposal and inability to maintain cold chain or relying on less specialized transport methods raise grave sterility concerns. The choice of injection settings demonstrates a dedication to sterility, with 63% choosing primary operating rooms. However, 5% of practitioners use outpatient clinics, highlighting the hazards associated with less supervised situations. Adherence to infection control measures, such as wearing masks (84%), sterile gloves (88%), and povidone-iodine preparation (87% for periocular skin, 90% for conjunctiva), appears to be strong, showing a general emphasis on patient safety.

Most of the ophthalmologists (61%) in our study take systemic history before injecting IVI, which is crucial, as it is contraindicated in certain conditions like recent CVA or pregnancy. While IVIs are associated with known local adverse effects, such as infective endophthalmitis, intraocular inflammation, ocular hemorrhage, rhegmatogenous retinal detachment, and transient elevation of intraocular pressure, systemic side effects including thromboembolic events, myocardial infarction, stroke, hypertension, gastrointestinal perforations, and kidney disease, though rare, have been reported in the literature.[17-19] Notably, systemic side effects have been found to be somewhat more frequent with Bevacizumab, likely due to its slightly higher systemic absorption.[20] Nearly half of the respondents (47%) checking random blood glucose levels before injecting IVI is a rather interesting finding since its correlation with systemic or ocular side effects haven't been reported in literature.

Our finding that only 48% of ophthalmologists obtain special pre-injection informed consent raises significant concerns and suggests a substantial gap between local practice and international standards. The RCOphth's 2024 guidance emphasizes that informed consent for intravitreal injections must document all material risks, and any drug change—including off-label bevacizumab use—should be recorded with evidence of patient discussion.[21] Given DRAP's ban in Punjab on IVI Avastin® in 2023, it is essential that patients are fully informed about the off-label use of anti-VEGF agents and the associated risks and complications of other IVIs. This gap in consent practices suggests that some patients may not be fully aware of these important factors, highlighting the need for standardized protocols to enhance transparency and ensure patient safety as stated by Ali *et al*.[22]

The challenges we documented, from inconsistent protocols to the economic fallout of the bevacizumab ban, are not unique to Pakistan. They reflect systemic barriers prevalent across low- and middle-income countries, as systematically outlined by one study.[23] In their review, cost constraints, ophthalmologist shortages, inequitable resource distribution, poor patient awareness, and inadequate infrastructure emerged as recurring themes. The interventions they advocate—including strategic use of low-cost therapies, enhanced training initiatives, national action frameworks, and prospective data collection—are directly applicable to Pakistan.

LIMITATIONS OF STUDY

This study has several limitations. First, the sample of 100 respondents, while sufficient for descriptive analysis, represents only a small proportion of active PVRS members, and the use of convenience sampling may have introduced selection bias. Second, the data are self-reported, which raises the possibility of recall or social desirability bias, although anonymity was preserved to mitigate this concern. Third, the finding that outcomes worsened following the bevacizumab ban reflects physicians' subjective impressions rather than objective clinical measures, and this should be taken into account when interpreting the results.

CONCLUSION

Our study demonstrates that there is considerable heterogeneity regarding IVI practice patterns across Pakistan. The ban on bevacizumab exposed critical systemic vulnerabilities, including an over-reliance on a single low-cost agent, the absence of standardized aseptic techniques, protocols of compounding and injecting, and significant ethical breaches in the informed consent process. By identifying existing gaps and inconsistencies, these findings

may contribute to the development of standardized national guidelines and sustainable access strategies, ensuring equitable and safe retinal care in Pakistan.

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Discolure:

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MS & FS: Data acquisition, data analysis, critical review, approval of the final version to be published.

MA & HF: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

YA & SZ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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