All India Ophthalmological Society members’ survey: Practice pattern of intravitreal anti-vascular endothelial growth factor injection

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Purpose: The aim of this paper is to report the results of an on-line survey to evaluate the practice pattern of Indian retina specialists in administering intravitreal anti-vascular endothelial growth factor injection.

Methods: A structured questionnaire on the intravitreal injection (IVI) procedure protocols was sent online to all members of the All India Ophthalmological Society (AIOS) with a request to the retina specialists to respond. A unique link that directed to the web-based questionnaire page allowed a single response only. Participating physicians were masked from each others’ responses. The responses were categorized into pre-injection patient preparation, injection aliquoting, injection administration, and post-injection care. The results were compared with similar surveys in Europe, the UK, and the USA. Results: Response was received from 741 of 1016 (73%) retina specialists (of 16,000 AIOS ophthalmologists). The survey showed: 43.5% evaluated patient’s cardiac risk factors, 60% used prophylactic topical antibiotic, 90.9% performed injection under topical anesthesia, 55% aliquoted from the bevacizumab vial at the eye care facility, 66.2% used a single puncture technique, 91.4% injected in the main operating room, 98% wore masks and sterile gloves during the procedure, 96% used lid speculum, and 89.3% advised topical antibiotic after the procedure. Peri-procedure antibiotic use, injection in the main operating room, wearing of gloves and mask were higher than practices in other countries. Conclusion: Ophthalmologists in India practice asepsis in IVI procedure. There is no uniform protocol for aliquoting bevacizumab. Single use bevacizumab vial for exclusive ophthalmic use will further improve the safety of the procedure.

Key words: Bevacizumab, endophthalmitis, intravitreal injection, practice pattern

Intravitreal injection (IVI) is the standard of care in many ophthalmic conditions. The number of IVI is rising in North America[1] and Europe.[2-3] Of a variety of IVIs including antibiotics, corticosteroids, and anti vascular endothelial growth factors (VEGF), the latter outnumbers the others. Intravitreal anti-VEGFs are mostly given in age-related macular degeneration or its variants and retinal vascular lesions including diabetic macular edema. Of the three available anti-VEGF molecules, bevacizumab, ranibizumab, and aflibercept, the former is used more often than the other two molecules.[4-5] In order to improve safety and prevent injection procedure-related adverse events, there are published guidelines including the ones from the Vitreo Retinal Society of India (VRSI).[6]

However, the practice pattern of IVI of anti-VEGFs varies from practice to practice and from country to country. The latest one is the European practice and consensus on the use of anti-VEGF published in 2018.[7] Similar data or consensus is not available from India. This paper describes the results of an on-line survey of ophthalmologists in India, predominantly involving the retina specialists, on the practice patterns in IVI procedures of bevacizumab (Avastin, Genentech, San Francisco, CA, USA).

Methods

The survey was conducted among the retina specialists from member pool of All India Ophthalmological Society (AIOS). The questionnaire was prepared considering the current practice pattern and previous literature survey by experienced retina specialists (JC, TD, AK). The questionnaire included 17 questions on the patient preparation, drug procurement, injection procedure, and post injection care. (Supplement 1). After consulting with the institutional ethics committee, the study was considered to be eligible for exemption.

A link was sent to 16,000 ophthalmologists across India on their e-mail addresses associated with AIOS, which directed to a web-based questionnaire page – Google forms with secure confidential access. The e-mail explained the study goals, details, instructions, and contact details of the investigators. Participating ophthalmologists were masked from each other about their personal details and responses. Before submitting,

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participants could modify their responses. Each user was allowed a single response. There was provision to skip a question without choosing one of the response options. Once submitted, there was no opportunity to change the responses. This methodology was similar to one used in the previous retina technology and trend survey in the Asia Pacific region and cataract surgery prophylaxis survey in India.\[8,9\] Three reminders were sent over one month before giving up the non responder.

**Results**

The response rate was 72.9% (741 of 1016 retina specialists of 16,000 ophthalmologists members of the AIOS) across the county. The responses obtained were categorized under the following sections: Pre-injection patient preparation, injection preparation, injection administration, and post-injection care. Around three-quarter of times (77%, 532/691 responses) retina specialists performed the intravitreal injections at their centers.

**Pre-injection practices**

While evaluating the systemic risk factors, 43.5% (299/688 responses) ophthalmologists routinely evaluated the cardiac risk factors; and 38% (261/688 responses) checked random or fasting blood glucose levels for their patients. Almost 82% (563/690 responses) would expect random blood sugar (RBS) values less than 200 mg/dl before the IVIs. A majority (80%, 531/664 responses) of the ophthalmologists obtained special informed consent from their patients specifying the off label use of bevacizumab. Only 60% (431/722 responses) of ophthalmologists preferred using prophylactic antibiotics; 91% (641/706 responses) of ophthalmologists used topical anesthesia for IVIs.

**Injection preparation**

At least half of the respondents (55%, 362/658 responses) aliquoted bevacizumab at their own eye care facility; 14.4% (95/658 responses) obtained the aliquots from another centre. Nearly 12.5% (82/658 responses) ophthalmologists preferred pooling their patients on a single day and used one bevacizumab vial by single or multiple punctures. Majority, 66.2% (428/647 responses) used single puncture for preparing aliquots from the bevacizumab vial, and 19.5% (126/647 responses) punctured the vial multiple times. Nearly all, 96.1% (585/609 responses) stored the opened vials and the loaded syringes in the refrigerator. The time period of its usage was variable: Of 639 responses, 39.8% (n = 254) used it within few hours, 21.3% (n = 136) used by one week, 20% (n = 128) used by two weeks, and 18.9% (n = 120) used by one month. The cold chain was maintained at all levels either by refrigerators or icepacks.

**Injection administration**

A majority (91.4%, 650/712 responses) of ophthalmologists performed IVIs in the main operating room and 8% (57/712 responses) conducted the procedure in the minor operating rooms. A small number of ophthalmologists, fewer than 2% (12/712), would prefer outpatient clinics for IVIs. Most of the respondents (98%, 702/715 responses) wear masks and most (98%, 701/717 responses) would ensure that the circulating technical staffs in the sterile operating area also wear masks during IVIs. Similarly, 98% (700/718 responses) wore sterile gloves and 95.9% (681/711 responses) used eyelid speculum during IVIs.

**Post-injection care**

Three-fourths (77.3%, 555/718 responses) ophthalmologists would advise eye patching immediately after the procedure and 89.3% (642/719 responses) used antibiotics for a short period after IVI. Nearly 58% (410/707 responses) ophthalmologists would not advise restrictions for their patients. Two-third (66.6%, 468/703 responses) ophthalmologists admitted to review their patients the following day, and 18.3% (129/703 responses) would review a week later.

The results of the survey are compared with the similar surveys in Europe, the USA, and the UK. [Table 1]\[7,10,11\]

**Discussion**

This is the first survey in India to analyze the practice patterns of intravitreal bevacizumab. Similar surveys have been conducted in the United States of America, the United Kingdom, Europe, and Israel.\[10-13\] This survey, though concerned intravitreal bevacizumab only, would also apply to practice pattern of other intravitreal injections- antibiotics, other anti-VEGF molecules and corticosteroid, other than the preparation of the injection itself. Currently, bevacizumab is dispensed in a larger volume vial and needs aliquoting for ophthalmic use.

Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF A).\[14\] VEGF-A is a growth factor protein that stimulates angiogenesis in many diseases. In ophthalmology, it is used in a variety of retinal diseases, from age-related macular degeneration to retinal vascular diseases.\[15\] However, the drug is not without side effects, particularly in vulnerable people with advanced age, cardiovascular, and cerebro vascular diseases.\[16\] Our survey indicated that less than half of the respondents, 43.5%, routinely check for cardiovascular risk-factors before IVIs.

The most devastating ocular complication following IVI is the occurrence of endophthalmitis\[17,18\] and sinister one is the occurrence of cluster endophthalmitis.\[19\] The essential recommendations as per various guidelines are to wear gloves and mask, and use lid speculum to prevent eyelashes in the injecting field.\[16\] The survey showed that between 95% and 98% ophthalmologists follow these instructions in India. But while it is documented that operating rooms are not mandatory for IVIs,\[6,21\] over 90% ophthalmologists in India chose to perform the IVIs in the main operating room. This is probably related to the uncertain sterile conditions in the outpatient clinics and offices.

One of the important factors in intravitreal bevacizumab is its preparation. To date, it is not available as single use vial for ophthalmic use. In the absence of certified compounding pharmacy in India, the eye care facilities and individual ophthalmologists have adopted their indigenous aliquoting techniques. The current survey showed that half of the respondents (55%) prepare aliquots in their own facility and nearly 20% ophthalmologists perform multiple puncture technique for loading from the bevacizumab vial. An earlier report has recorded that a quarter of ophthalmologists in the Asia Pacific region use multiple pricks bevacizumab vial for lack of compounding pharmacy in their country.\[22\] Only 39.8%
of the respondents used the vial within few hours. Around 18.9% almost used the same vial for a month. Saoji et al.[20] and das et al.[21] have reported safety and efficacy in using single use bevazicumab vials for almost a week provided the vials are stored in a refrigerator at 4 degree Celsius.

There is no robust evidence regarding the complications associated with poor glycemic control in the invasive ocular procedures.[22] The VRSI guidelines suggest to defer IVIs in uncontrolled diabetes.[6] Nearly half of the ophthalmologists, 43.5%, take note of the random blood sugar (RBS) and over three quarters, 80%, of them considered RBS safe when it was less than 200 mg/dl. However, glycated hemoglobin (HbA1c) rather than RBS is considered a better indicator for ambulatory surgery in the UK.[22]

The other large deviation in Indian ophthalmologists practice was with the extra cautious usage of peri-procedure topical antibiotics (60% – pre IVI period, and 89.3% – post IVI period). This is in contrast to the peri-procedure antibiotic practice among ophthalmologists across Europe (67%), the USA (34% pre IVI and 81% post IVI), and the Asia-pacific region (39%).[13,12]

The study did not collect data from the non retina specialists who might also be performing intravitreal bevacizumab. There are debates and/or published data of general ophthalmologists and trained nurses practicing intravitreal anti VEGF injections in the USA[23] and the UK,[24,25] respectively. While we could state with certainty that the nurses are not practicing intravitreal injections in India, the same can not be said for general ophthalmologists. Other study limitations are its lack of information concerning usage of eye drapes, types of globe softening techniques being practised, method of capping the aliquoted syringes, and the prevalence of simultaneous bilateral injections.

This survey mainly throws light on the practice patterns in administering IVIs but from the limited data obtained on injection preparation methods it also reinforces the fact that difficulties exist in maintaining sterility while preparing aliquots and in administering bevacizumab. There is no certified compounding pharmacy in India and many of the recommendations such as maintaining a class 10 environment in the preparation of bevacizumab aliquots becomes less practical. Considering the facts that bevacizumab is as efficacious as ranibizumab,[26,27] it is more cost-effective,[28,29] it is the more often used anti-VEGF molecule,[30] and it is a World Health Organization (WHO) listed essential drugs in ophthalmology,[31] it is time that the manufacturing companies dispense single-use bevacizumab vials for ophthalmic use. It is also possible that bio-similar of these anti-VEGF molecules would replace the original molecules as the patent expires in coming few years.[32] However, this does not reduce the responsibility of all ophthalmologists in practicing a safe protocol for IVIs particularly in aliquoting bevacizumab till such time that single use vials are available for ophthalmic use.

**Conclusion**

This survey of ophthalmologists in India showed that they practice asepsis in IVI procedure. However, there is no uniform protocol for aliquoting bevacizumab. Single use bevacizumab for exclusive ophthalmic use will further improve the safety of the procedure.

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**Conflicts of interest**

There are no conflicts of interest.
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### Questionnaire

1. Do you use pre-injection prophylactic antibiotics?
   - a. Yes
   - b. No
   - c. Sometimes
   - d. Other
2. Do you use post-injection prophylactic antibiotics?
   - a. Yes
   - b. No
   - c. Sometimes
   - d. Other
3. Do you patch the eye after injection?
   - a. Yes
   - b. No
   - c. Sometimes
   - d. Other
4. Do you advice any restriction after injection during the post-operative period?
   - a. No
   - b. Yes, please explain
   - c. Other
5. Do you wear mask during the injection?
   - a. Yes
   - b. No
   - c. Other
6. Does your circulating staff in the operating room wear mask during the injection procedure?
   - a. Yes
   - b. No
   - c. Other
7. Do you wear gloves during the injection?
   - a. Yes
   - b. No
   - c. Other
8. How do you acquire intravitreal bevacizumab injections?
   - a. Aliquot at your clinic
   - b. Acquire aliquoted injections from someone else in the city
   - c. Pool your patients in someone else’s clinic and give injections
   - d. Other
9. How do you prepare intra-vitreal bevacizumab injections?
   - a. Multiple puncture on the same day
   - b. Single puncture and prepare syringes under aseptic conditions
   - c. Other
10. How long do you keep the injection after preparation or vial after opening?
    - a. Few hours
    - b. 1 week
    - c. 2 weeks
    - d. 1 month
11. When do you review your patients after injection?
    - a. Next day
    - b. At one week
    - c. At one month
    - d. Other
12. How do you maintain cold chain?
    - Your answer:
13. How do you take a “special” consent for off label intra-vitreal injections?
    - a. Yes, the one available at AIOS website
    - b. Yes, on a different consent made by you for off label injections
    - c. No
    - d. Other
14. How do you evaluate systemically your patients before intra-vitreal injections?
   a. Never evaluate systemically
   b. Check Random/Fasting sugar only
   c. Cardiac evaluation if risk factors are present
   d. Other
15. What is your cut-off for random sugars before intravitreal injections?
   a. 200
   b. 300
   c. Don’t consider before injection
   d. Other
16. Who administers the intra-vitreal injections at your clinic?
   a. Retina specialist
   b. Fellow
   c. Nurse
   d. Other: Injection site.
   e. Other
17. Which anesthesia you use for intravitreal anti-VEGF injections?
   a. Topical
   b. Subconjunctival
   c. Peri/retro bulbar
   d. pledget held on injection site.
   e. Other
18. Do you use eye speculum while injecting?
   a. Yes
   b. No
   c. Other
19. Where do you perform injection procedure?
   a. In the main operating room
   b. In the minor operating room
   c. In the outpatient clinic
   d. Other:
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