

## Trend of Intravitreal Bevacizumab Dispensing Technique in Nepal

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### ABSTRACT

**Introduction:** The main purpose of this survey was to find out what technique for bevacizumab injection is practiced by ophthalmologists in Nepal and to evaluate which is the best technique of drug dispensing and what possible hindrances are there in following it.

**Materials and methods:** This was an online survey using google forms.

**Results:** There were a total of 34 participants in the survey. Most of the participants (58.8%) followed the same vial, multiple prick, multiple days method for giving intravitreal bevacizumab.. Majority of participants said they thought that aliquoting the drug and using it same day would be the best technique to prevent post injection endophthalmitis. Cost and unsuitability for small hospitals were the main factor preventing surgeons from practicing the best method.

**Conclusion:** Risk of endophthalmitis can be reduced by following proper drug dispensing techniques. Aliquoting bevacizumab in smaller syringes under aseptic conditions can reduce the risk of endophthalmitis.

**Key words:** Intravitreal, Endophthalmitis, Questionnaire, Bevacizumab.

### INTRODUCTION

Anti VEGFs have become an indispensable tool for management of various retinal vascular diseases. The most commonly used anti VEGFs are bevacizumab, ranibizumab and aflibercept. Although bevacizumab was the first anti VEGF to be used clinically, it is still not FDA approved

for intraocular use. Most of the major studies including CATT trials have shown that both bevacizumab and ranibizumab are equally effective in managing retinal vascular entities (Kodjikian et al, 2013; Krebs et al, 2013; Wells et al, 2015; Chakravarthy et al, 2012; Rosenfeld et al, 2005; Martin et al, 2012). It has been seen that off-label use of bevacizumab is more

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common than FDA approved ranibizumab, “cost” being the major driving factor (Dakin et al, 2014; Cohen et al, 2015). In fact, in developing countries like Nepal, bevacizumab is most commonly available and used as an anti VEGF. The safety profile of both the bevacizumab and ranibizumab have been found to be similar in long term studies (Martin et al, 2012; Ahfat et al, 2013). The incidence of post-intravitreal Bevacizumab endophthalmitis is 0.016 – 0.026% (Kumar et al, 2017). Commercially, bevacizumab is available as a 4 ml vial, which is then dispensed in smaller doses and used by ophthalmologists. The main technique for dispensing bevacizumab can be divided into four types: (a) single vial, multiple prick, multiple days - the vial is opened, drug is withdrawn with separate pricks for each patient. The vial is then stored in the refrigerator for 1 to 4 weeks and used as & when required. (b) same vial, multiple prick, same day - many patients are pooled in one day at same time, vial is opened and all patients are injected in one setting; (c) a vial is opened, drug is aliquoted into multiple

syringes under aseptic conditions, placed in double ETO packs and stored in refrigerator for use over 1 to 4 weeks; (d) drug is aliquoted in multiple syringes and packed but injected in one day and remaining syringes are discarded.

The main purpose of this survey was to find out what technique for bevacizumab injection is practiced by ophthalmologists in Nepal. We also evaluated which is the best technique ophthalmologists think and what possible hindrances are there in following it.

## MATERIALS AND METHODS

This study design was a non-interventional online multiple choice questionnaire survey. ‘Google forms’ was used for this purpose. All known retina practitioners in different parts of Nepal were enlisted. A link was generated and sent to all ophthalmologists registered with Nepal Medical Council. Each participant needed to answer four sets of questions as in Table 1.

**Table 1: Multiple choice questionnaire.**

S. No	Questions	Options
1	What method do you practice for giving bevacizumab injection?	a. Same vial, multiple prick, multiple days. b. Same vial, multiple prick, single day. c. Drug aliquoted, packed and stored for use on multiple days. d. Drug aliquoted and all aliquots used on same day.
2	Which method you think is ‘BEST’ (to prevent post injection endophthalmitis)?	a. Same vial, multiple prick, multiple days. b. Same vial, multiple prick, single day. c. Drug aliquoted, packed and stored for use on multiple days. d. Drug aliquoted and all aliquots used on same day. e. No scientifically proven method.

3	If you have chosen different options for the first two questions, what do you think is the main hindrance in practicing the best method?	<ul style="list-style-type: none"> <li>a. Too expensive.</li> <li>b. Cumbersome.</li> <li>c. Not suitable for small hospitals.</li> <li>d. Do not know the exact procedure.</li> <li>e. Drug allocation and packing on a small scale is difficult.</li> </ul>
4	In case you use the same vial for multiple days, how long do you store the drug?	<ul style="list-style-type: none"> <li>a. Upto 1 week.</li> <li>b. Upto 2 weeks.</li> <li>c. Upto 3 weeks.</li> <li>d. Upto 4 weeks.</li> </ul>

## RESULTS

There were a total of 34 participants in the survey. Most of the participants (58.8%) said that they followed procedure (a); followed by procedure (b), (d) and (c) in that order (Figure 1). Majority of participants said that (d) is

the best method to give intravitreal injections (Figure 2). Cost and unsuitability for small hospitals were the main factor preventing surgeons from practicing the best method (Figure 3). For multiple day use, most retina practitioners preferred to discard the vial after 1 week (Figure 4).

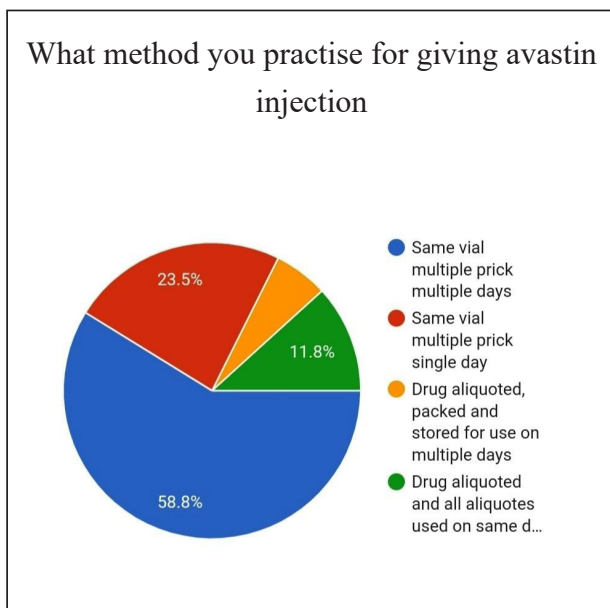


Figure 1

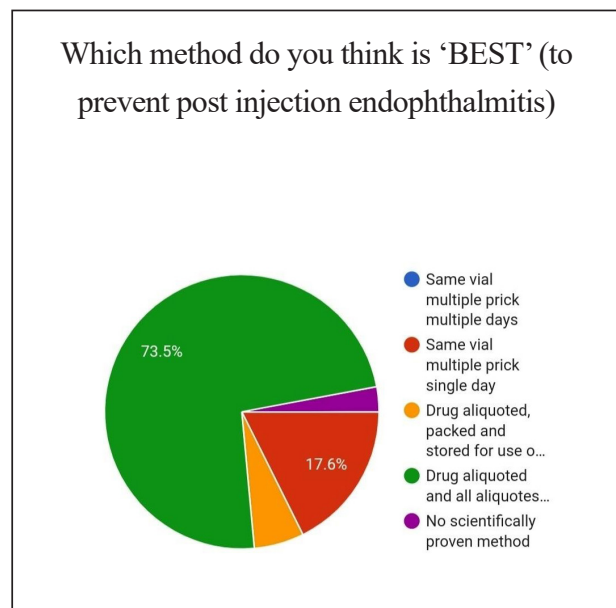


Figure 2

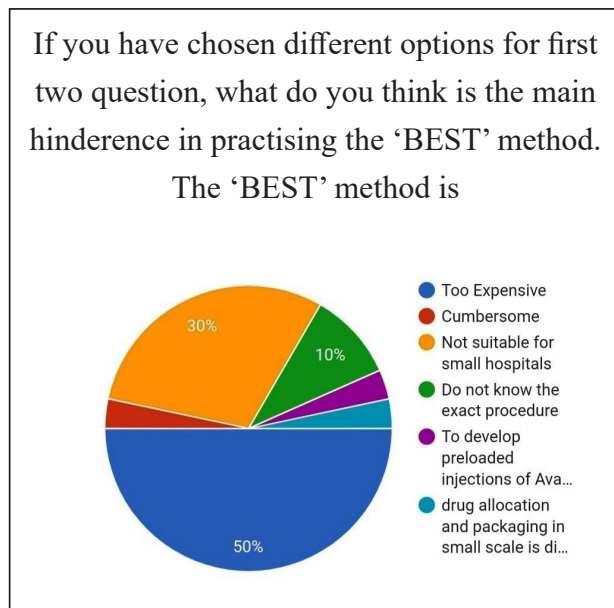


Figure 3

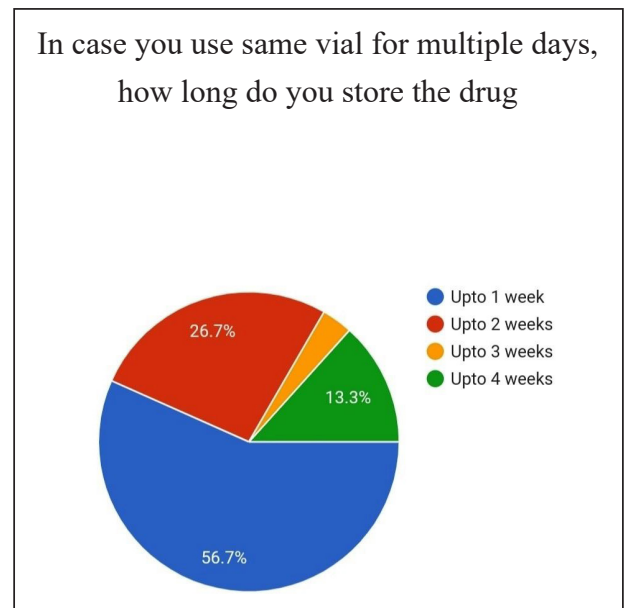


Figure 4

## DISCUSSION

Even though intraocular injection is a safe procedure, it is not devoid of complications. The main complication which ophthalmologists are more concerned with is endophthalmitis. Although incidences of cluster endophthalmitis have been reported more often with bevacizumab, the main cause for this is drug dispensing technique rather than drug compound itself (Omic et al,2014). As bevacizumab is not FDA approved, it is not available for single use. It is available in larger vials available for intravenous use, which are then divided into smaller doses for ophthalmic use. It is this step that is the major concern as a source of infection. Since this is not an FDA approved drug for ophthalmic use, there is no common consensus regarding which is the best technique for drug dispensing. Ophthalmologists follow different drug dispensing techniques based on

various factors: cost, convenience, availability, patient population, storage facility etc. An ideal technique would be one which is cheap, convenient and has the least risk of infection.

In this survey, procedure (a) was the most commonly followed technique by surgeons in Nepal. This seems to be in accordance with many parts of the world, especially in developing countries. This technique is best suitable for smaller hospitals where there is no ETO facility and where only a few patients need injections on a daily basis. Discarding the vial after single use would not be economical in this setting. The vial is stored in a refrigerator which can have an aseptic environment. Also, there is no clear recommendation as to how long the drug can be stored and its efficacy after opening the vial. Usually, the drug is stored for 4 weeks or even more. 56.7 % of respondents discarded the drug after 1 week, but 13.3 % stored the drug till 4

weeks. Although maintaining the cold chain and sterility is difficult, most surgeons tend to follow this technique as it is most cost effective.

To prevent the above complications, many surgeons prefer technique (b) wherein the patients are pooled and injected in one setting. The remaining drug is discarded which reduces storage-related complications. In this survey, 23.5 % followed this technique. The main drawback of this technique is that sometimes it may be cumbersome and impractical to call all patients in one day. If the patient misses the day due to any reason, he would have to wait for another schedule which would unnecessarily delay his treatment. Since many patients are injected at one time, if infection occurs, it can turn into large cluster endophthalmitis. Cluster endophthalmitis has been reported after avastin use in many parts of the world. Khan et al, 2016, reported an incidence of cluster endophthalmitis in 2016 where six out of eight patients developed endophthalmitis after getting bevacizumab from a single vial. Drugs controller governor of India had temporarily banned bevacizumab use after a similar incident (Kumar et al, 2017).

The third technique (c) is to ETO pack drugs in small syringes and store them. This reduces the risk of multiple punctures. This also reduces the cost as syringes can be stored for a few weeks and less drug is wasted. The All India Ophthalmological Society recommended this technique in their guideline to reduce endophthalmitis risk (Kumar et al, 2017). However, this was the least followed technique (5.9%) in this survey. The likely reason here seems to be the unavailability of ETO facilities

in many hospitals. 10% participants also said that there was ambiguity regarding the exact technique of ETO packing under aseptic conditions.

The fourth technique (d) is to aliquot the drug under aseptic conditions and use the syringes on the same day. This reduces the complication of multiple punctures and storage. Only 11.8 % followed this technique, but 73.5% of retina practitioners thought that this is the best technique of giving bevacizumab injection. It still has some problems mentioned with technique (b). When asked what were the main hindrances in following the best technique, most said that cost and unsuitability for smaller hospitals were major factors. Other causes were confusion regarding the exact procedure and cumbersome technique.

## CONCLUSION

Bevacizumab is found to be comparable with other anti VEGFs in terms of efficacy and safety profile. But the problem with this drug is lack of guidelines and common consensus in ophthalmic use as this drug lacks FDA approval. Nevertheless, this is definitely the most cost-effective anti VEGF in ophthalmic scenario in Nepal. Also, aliquoting bevacizumab in small syringes under aseptic conditions can reduce risk of endophthalmitis. The less the drug is stored the better it is for safety and efficacy issues. Technique (d) can be considered an ideal technique in the present situation. But surgeons can also follow technique (c) which is more economical.



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