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Research Article

Comparison of the Syringe Preparation Time for Ranibizumab Prefilled Syringe versus Bevacizumab, Ranibizumab, and Aflibercept Vials

Ahmet Mehmet Somuncu[1], Adem Uğurlu[2], Nurdan Gamze Taşlı[1], Yücel Karakurt[2], İbrahim Çiçek[2]

[1]Clinic of Ophthalmology, University of Health Sciences Türkiye, Kanuni Training and Research Hospital, Trabzon, Türkiye
[2]Deparment of Ophthalmology, Erzincan Binali Yıldırım University Faculty of Medicine, Erzincan, Türkiye

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ORCID IDs of the authors: A.M.S. 0009-0008-0304-5278, A.U. 0000-0002-8900-7043, N.G.T. 0000-0001-8587-3430, Y.K. 0000-0001-8104-3819, İ.Ç. 0000-0003-3297-1568.

ABSTRACT

Objective: To compare the syringe preparation time for ranibizumab prefilled syringe versus bevacizumab, ranibizumab, and aflibercept vials in routine retinal practice.

Methods: The study was conducted retrospectively between July 2019 and February 2021 at the Ophthalmology Department of the Erzincan Binali Yıldırım University Faculty of Medicine, Türkiye. Syringe preparation times for 157 eyes were collected for the study. For each injection, one independent observer recorded the duration of each step required to prepare the syringe, starting with the removal of the ranibizumab prefilled syringe or bevacizumab, ranibizumab, and aflibercept vials from their respective packaging, and ending at the moment the dose was ready for injection. Injections were excluded if disruptions during the drug administration process were due to external factors or if other errors occurred in measuring preparation time. In addition to preparation time, formation of air bubbles during syringe preparation was qualitatively observed.

Results: Forty-five eyes were treated with the ranibizumab prefilled syringe, while bevacizumab, ranibizumab, and aflibercept vials were used to treat 40, 36, and 36 eyes, respectively. The mean injection preparation time was 46.5±4.8 s for the syringe and 66.1±7.2 s, 64.2±5.1 s, and 74.7±8.5 s for the bevacizumab, ranibizumab, and aflibercept vials, respectively. Air bubble formation was more frequently observed in the vial groups, particularly in the aflibercept group, than in the prefilled syringe group.

Conclusion: The ranibizumab-prefilled syringe required fewer preparation steps and had a lower incidence of bubble formation compared with other vials. Specifically, when preparing the aflibercept vial for injection, dose adjustment took longer than for the bevacizumab and ranibizumab vials, primarily due to air bubbles.

Keywords: Ranibizumab, prefilled syringe, preparation time, vial

INTRODUCTION

Anti-vascular endothelial growth factor (VEGF) drugs are developed to bind to and inhibit VEGF, which is believed to play a key role in the formation of new blood vessels. Randomised clinical trials have shown that intravitreal administration of these drugs is effective in the treatment of retinal diseases such as diabetic retinopathy, retinal vein occlusion and exudative age-related macular degeneration.[1] It has been shown that the intravitreal injection of anti-VEGF is effective in treating some retinal diseases and improving their prognosis. In addition, research indicates that anti-VEGF therapy helps prevent visual loss and improve vision.[2-4]

Anti-VEGF treatment is becoming increasingly widespread and includes the administration of intravitreal injections.[5,6]

Corresponding author: Ahmet Mehmet Somuncu, **E-mail:** mehmetsomuncu89@hotmail.com

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The number of patients receiving intravitreal injections in the USA increased from over 4 million in 2013 to nearly 6 million in 2016.[7] However, this therapy requires frequent follow-up examinations. In addition, more patients are becoming eligible for this treatment compared to previous surgical procedures, resulting in an additional workload.[8-11] To accommodate the growing patient population requiring anti-VEGF therapy and to reduce the risk of complications, pre-injection preparation time should be minimized. Nevertheless, some diseases, such as endophthalmitis, still pose certain safety risks due to the invasive nature of the treatment.[12]

In 2013, the EU granted approval for the use of ranibizumab solution in pre-filled syringe injections (PFSs) for the treatment of visual impairment caused by neovascular age-related macular degeneration , diabetic macular edema, retinal vein occlusion, pathological myopia. The use of intravitreal Ranibizumab 0.3 mg PFS for the treatment of diabetic retinopathy and diabetic macular edema was approved by the US Food and Drug Administration in March 2018.[13,14]

PFS solutions have the same formulation as their vial counterparts (a single intravitreal injection of 0.5 mg delivered in a 0.05 mL volume). They have a latex-free, non-retractable plunger and a small, minimally siliconised barrel with a low void volume. Additionally, PFSs are packaged in sterile, disposable trays.

We aimed to compare intravitreal injection preparation times between the ranibizumab PFS and the vials of ranibizumab, bevacizumab, and aflibercept in routine clinical practice.

MATERIALS AND METHODS

The study was an observational, cross-sectional study conducted in the Department of Ophthalmology, Erzincan Binali Yıldırım University Faculty of Medicine, between July 2019 and February 2021. Ethical approval was obtained from the ethics committee of Erzincan Binali Yıldırım University Faculty of Medicine (E-21142744-804.99-138855**;** date: 17.01.2022) and the principles stated in the Declaration of Helsinki were followed in the study. Since the study involved only observation of clinical practices without collecting identifiable patient data, informed consent for participation was not obtained.

In addition to preparation time, the occurrence of air bubble formation during syringe preparation was qualitatively observed by the same independent observer.

MAIN POINTS

- The frequency of anti-vascular endothelial growth factor (VEGF) injections has been increasing, and they are being evaluated as treatment options for numerous diseases.
- However, anti-VEGF injections require a preparation time, and as this time increases, the risk of contamination and, consequently, of endophthalmitis increases.
- Therefore, we believe that determining the biological agent with the shortest preparation time and comparing the preparation time of the Ranibizumab Prefilled Syringe with those of other anti-VEGF agents used in clinical practice will contribute to the literature.

Data on syringe preparation time were gathered from 157 eyes. For each injection, one independent observer recorded the duration of each step required to prepare the syringe, starting with the removal of the ranibizumab-prefilled syringe or vials of bevacizumab, ranibizumab, and aflibercept from their respective packaging and ending when the dose was ready for injection.

Six injection-preparation steps were identified when using vials of bevacizumab, ranibizumab, and aflibercept: 1) removal of the contents from the external box and internal packaging; 2) donning gloves; 3) attaching a filter needle; 4) extracting the solution from the vial using the filter needle; 5) removing the filter needle and attaching the injection needle; and 6) adjusting the dose. In contrast, four injection-preparation steps were identified when using the ranibizumab-prefilled syringe: 1) the removal of contents from the external box and internal packaging, 2) the donning of gloves, 3) the removal of the syringe cap and the attachment of the injection needle, and 4) the adjustment of the dose.

Exclusion Criteria

Injections were excluded if disruptions occurred during the drug administration process due to external factors or if other errors occurred in measuring preparation time.

Statistical Analysis

The data were analysed using the Statistical Package for the Social Sciences (IBM SPSS) version 22.0. Descriptive statistics are presented using means and standard deviations for measured data. The Shapiro-Wilk test was used to assess whether the measured data were normally distributed. The Mann-Whitney U test was used to compare the measured data. The level of significance was set at $P < 0.05$.

RESULTS

No cases of endophthalmitis were observed in any group.

Forty-five eyes were treated with the ranibizumab prefilled syringe, while bevacizumab, ranibizumab, and aflibercept vials were used to treat 40, 36, and 36 eyes, respectively. The mean injection preparation time was 46.5 ± 4.8 s for the ranibizumab prefilled syringe and 66.1 ± 7.2 s, 64.2 ± 5.1 s, and 74.7 ± 8.5 s for the bevacizumab, ranibizumab, and aflibercept vials, respectively. The injection preparation time was significantly lower in the ranibizumab prefilled syringe group. The preparation time for the aflibercept vial was significantly longer than that for the other intravitreal drugs under investigation (Table 1). No findings of endophthalmitis were encountered in any patient who received the injection (Table 2).

DISCUSSION

A limitation of this study is that silicone-induced symptoms were not evaluated, and future studies may investigate these symptoms.

This study demonstrated a significant reduction in syringe preparation time and bubble formation when using the ranibizumab PFS vial compared to other vials. In particular,

when preparing the aflibercept vial for injection, the dose-adjustment process took longer than that for the bevacizumab and ranibizumab vials, primarily due to bubble formation. With the PFS form, the administering physician was less dependent on a nurse's continuous presence during injection preparation.

Drugs in the form of PFS have been used for many years in various medical treatments. Similar to previous studies on insulin and heparin PFSs, PFSs have been shown to be beneficial in terms of speed of delivery, reducing the complexity of syringe preparation, time efficiency and user satisfaction.[15,16] Kasi et al.[17] reported that PFSs also increased safety in vaccination versus traditional vials, as they involved fewer handling errors.

Ranibizumab PFS is a novel intravitreal anti-VEGF agent used to treat retinal diseases, including diabetic retinopathy, retinal vein occlusion, and exudative macular degeneration. The use of PFS requires less time and eliminates several procedural steps, including attachment and removal of the aspiration needle and aspiration of the drug from the vial. Consequently, the user needs only to insert the injection needle into the PFS and adjust the dose.

Consistent with our study, Souied et al.[18] reported that the preparation time for intravitreal ranibizumab syringes using PFS was significantly shorter than with the vial. The authors found that the PFS resulted in a 17-29 s reduction in preparation time, similar to our findings (18-28 s). They also noted that the staff perceived a reduction in time spent addressing bubbles when using the PFS.[18]

Although air bubbles can form in the eye during intravitreal anti-VEGF injections, these bubbles are usually expected to be absorbed spontaneously within 3 days.[19-21] However, sometimes these bubbles can increase intraocular pressure when travelling at high altitudes, causing unexpected uncomfortable symptoms and even sudden loss of vision.[22] Similar to our findings, Sassalos and Paulus[23] demonstrated that the syringe design offers improved dose assurance and reduces injection time, the formation of air or silicone oil droplets and the risk of endophthalmitis by eliminating many steps in injection preparation. It has been observed that a solution of aflibercept has a higher viscosity than that of ranibizumab, which results in a greater propensity for the formation of bubbles and increased difficulty in their elimination.[24] The presence of bubbles poses a challenge since their injection into the vitreous can cause visual disturbances, leading to discomfort, fear of falling, and a reduced dose of the drug administered.[19]

According to our results, when preparing the aflibercept vial for injection, the dose adjustment process took longer than for the bevacizumab and ranibizumab vials because of bubble formation. Ranibizumab PFS features a Luer Lock design, which allows the needle to be gripped securely. The design of the PFS uses a siliconization process, called ''baked silicone'', in which an oil-in-water emulsion is spray-coated onto the inner surface of the syringe barrel and heat-fixed. This process minimises oil migration into the ranibizumab absolution and is expected to reduce the incidence of silicone-induced symptoms that may develop due to repeated intravitreal injections.[18] In addition to intraocular air bubbles, silicone oil droplets, which are thought to be associated with intravitreal anti-VEGF drug injections, have been detected in recent studies. Khurana et al. [25] showed that 1.7% of patients receiving bevacizumab prepared by an insulin syringe experienced silicone oil drip complications. This was attributed to dimethicone, a lubricant employed to reduce friction between the syringe body and the piston. Silicone oil droplets are assumed to resemble air bubbles in the eye and to cause floaters associated with water droplets. Although there are not enough studies on this subject in the literature, it is theoretically thought that these oil droplets may lead to the development of glaucoma.[26]

In a recent publication, Thompson highlighted the importance of utilizing silicone-free syringes for intravitreal injections, particularly in cases involving multiple regular anti-VEGF injections.[27] Melo et al.[28] reported that syringes without silicone oil performed best, in addition, the needles also contained silicone and this silicon oil may increase injection into the vitreous.

Lode et al.[29] described a novel method of pharmaceutical compounding using silicone-free syringes and an injection

Table 1. Preparation Times of Drugs

	Number of patients	Time (mean ± SD[1]) (s[2])	Min[3]	Max[4]
Ranibizumab prefilled syringe	45	46.5 ± 4.8	**41.7**	**51.3**
Bevacizumab vial	40	66.1 ± 7.2	**58.9**	**73.3**
Ranibizumab vial	36	64.2 ± 5.1	**59.1**	**69.3**
Aflibercept vial	36	74.7 ± 8.5	**66.2**	**83.2**

SD, standard deviation; s, second Min, minimum; Max, maximum

Table 2. The Development of Endophthalmitis In Patients Receiving Injections

	Number of patients	Endophthalmitis +	Endophthalmitis -
Ranibizumab prefilled syringe	45	0	45
Bevacizumab vial	40	0	40
Ranibizumab vial	36	0	36
Aflibercept vial	36	0	36

needle with a 33 G × 9 mm needle hub and low-dead-space. This method was evaluated for three widely used anti-VEGF biologics in ophthalmology: aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab (Lucentis). Building on their previous work, which detailed a compounding method for the repackaging and storage of aflibercept in silicone-oil-coated plastic syringes while maintaining drug stability and potency, the authors reported benefits, including enhanced safety and reduced time per patient. Combining anti-VEGF biologics allows single-dose vials to be divided into multiple syringes, considerably reducing waste and drug costs. These results suggest that compounding and storage of biologics for one week do not affect their functional activity. This allows safe and cost-effective compounding of anti-VEGF biologics into prefilled silicone oil-free syringes for intravitreal injection.

The proposed approach involves compounding anti-VEGF biologics and storing them in prefilled plastic syringes for intravitreal use. Additionally, bevacizumab is repackaged for ophthalmic use into small glass vials rather than plastic syringes. This innovative method aims to enhance safety and efficacy. Peterson et al.[30] reported that bevacizumab can be successfully packaged in small, single-dose glass vials for intravitreal injections. It was also stated that the properties of the product, including anti-VEGF bioactivity, would remain similar for 21 months under refrigerator storage conditions.[30] This approach warrants consideration as an alternative to plastic syringes for repackaging ophthalmic bevacizumab in small glass vials.

Endophthalmitis, a serious complication of intravitreal treatment that results in permanent vision loss, remains a significant concern in ophthalmic care. The utilisation of PFSs effectively eliminates numerous steps in the preparation of injections, thereby reducing the risk of iatrogenic contamination resulting from suboptimal drug or device handling.[18,31] Although no comparative study in the literature has proven this hypothesis, Storey's ongoing multicentre study suggests that the odds of endophthalmitis are lower with ranibizumab PFS than with conventional intravitreal injections. A large, multi-centered, retrospective study revealed that the use of PFS during intravitreal ranibizumab administration reduced the incidence of culture-positive endophthalmitis, and improved visual outcomes.[32]

In their multi-centre study, Souied et al.[18] demonstrated that the use of PFS resulted in a 25.5 second reduction in preparation time compared to the use of conventional syringes.[18] In our study, the mean injection preparation time was 46.5 ± 4.8 s for the ranibizumab prefilled syringe versus 66.1 ± 7.2 s, 64.2 ± 5.1 s, and 74.7 ± 8.5 s for the bevacizumab, ranibizumab, and aflibercept vials, respectively. Accordingly, injection preparation time was significantly lower in the ranibizumab prefilled syringe group and significantly higher for the aflibercept vial compared with the other intravitreal drugs.

Our findings, along with those from similar studies, reflect the common goal of shortening the preparation stages for intravitreal injections, thus reducing the total drug preparation time and, most importantly, minimizing the risk of infection. In the current study, the ranibizumab prefilled syringe required fewer preparation steps, enhancing ophthalmologists' work efficiency. This allows clinicians to see more patients per session, to reduce the total time required to see the same number of patients, to provide additional time for consultations when needed. In a busy retinal practice where several injections are performed per day, the use of PFSs could be a significant time-saver compared with vials. Although it is encouraging that no patient developed endophthalmitis in our study, we think that this finding may reflect the small sample size. Larger studies are needed on this subject.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the ethics committee of Erzincan Binali Yıldırım University Faculty of Medicine (E-21142744-804.99-138855, date: 17.01.2022)

Informed Consent: Since the study involved only observation of clinical practices without collecting identifiable patient data, informed consent for participation was not obtained.

Footnotes

Author Contributions

Concept Design – A.U., İ.Ç.; Data Collection or Processing – A.U., N.G.T, Y.K.; Analysis or Interpretation – A.U., İ.Ç. Literature Review – N.G.T, Y.K.; Writing, Reviewing and Editing – A.M.S.

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