

Accuracy, Precision, and Residual Volume of Commonly Used Syringes for Intravitreal Injections and the Impact on Intraocular Pressure

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Purpose: To compare accuracy, precision, and residual volume of commonly used syringes for intravitreal injections (IVIs) and to assess the intraocular pressure (IOP) rise by variations in volumes delivered.

Design: Experimental laboratory study.

Subjects: No subjects were involved in this study.

Methods: We tested 8 syringe models with 2 different needle setups, with 2 different solutions (distilled water or glycerin) and target volumes (50 and 70 μ L). To obtain the delivered and residual volumes, we weighed the syringe-needle setups with scale before liquid withdrawal, with liquid, and after liquid release. We also created an experimental eye model to determine the transient rise in IOP following stepwise 10- μ L increases in injection volumes.

Main Outcome Measures: Delivered and residual volumes, IOP rise.

Results: We tested a total of 600 syringe-needle setups. Becton Dickinson (BD) Ultra-Fine ($0.34 \pm 0.28 \mu$ L), Zero Residual ($1.53 \pm 1.15 \mu$ L), and Zero Residual Silicone Oil-free ($1.40 \pm 1.16 \mu$ L) syringes showed the lowest residual volume ($P < 0.001$) in comparison with the others (range: $24.86 \pm 1.78 \mu$ L for Injekt-F to $51.97 \pm 3.37 \mu$ L for Omnifix-F). The most accurate setups were (percentage deviation from target volume): Zero Residual Silicone Oil-free (+ 0.70%), Zero Residual 0.3 ml (+ 4.49%), BD Ultra-Fine (+ 7.83%), Injekt-F (9.42%), Norm-Ject (+ 15.88%), Omnifix-F (+ 16.96%), BD Plastipak Brazil (+17.96%), and BD Plastipak Spain syringes (+ 19.41%). There was a statistically significant difference between the Zero Residual Silicone Oil-free syringe and all other syringes ($P < 0.0001$), except for the Zero Residual 0.3-ml syringe ($P = 0.029$). The coefficient of variation was low for all syringes. The modeled IOP rise ranged from 32.3 (standard deviation [SD], 1.4) mmHg for 20- μ L injection volume to 76.5 (SD, 1.0) mmHg for 80- μ L injection volume. For the standard 50- μ L injection volume, the peak pressure was 50.7 (SD, 0.1) mmHg, and the pressure rise duration was 28 (SD, 2) minutes.

Conclusions: There were significant differences in accuracy and residual volume between syringes, whereas they showed a high precision. Volume excess results in a considerable increase in IOP rise after injection. These findings may provide a relevant overview to clinicians and to both device and drug manufacturers regarding pharmacoeconomic, safety, and efficacy issues.

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Among the various ophthalmic procedures currently performed worldwide, intravitreal injections (IVIs) of anti-VEGF are unquestionably among the most common. Conditions such as age-related macular degeneration, diabetic macular edema, and macular edema because of retinal vein occlusion have IVI of antibody-based biologics as their main therapeutic arsenal, and these treatments often involve long-term repeated injections and prolonged follow-up.^{1,2}

Most injections are still performed with syringes and needles not developed for ocular usage.³⁻⁶ Considering the small volumes required in IVI (50 μ L for the commonly used anti-VEGF biologics), a special concern arises with regard to accuracy and precision of the devices. Interestingly, studies conducted in recent years have shown that the doses delivered to patients are higher than expected in most cases.^{7,8} This lack of accuracy and precision, with a clear

tendency toward overdelivery, may have clinical implications. A recent meta-analysis concluded that long-term IVI was associated with diminishment of the retinal nerve fiber layer thickness, and although the clinical relevance of this finding remains to be resolved, caution should be exercised when administering IVI to patients with glaucoma in particular.⁹

Several studies have addressed factors that may influence the magnitude of intraocular pressure (IOP) elevation after IVI, such as lens status, axial length, ocular rigidity, presence of glaucoma, cumulative numbers of IVI, frequency of IVI, and choice of anti-VEGF drug.¹⁰ The literature, however, places little emphasis on fluid volume, assuming injection of the standard 0.05 ml of anti-VEGF. It was

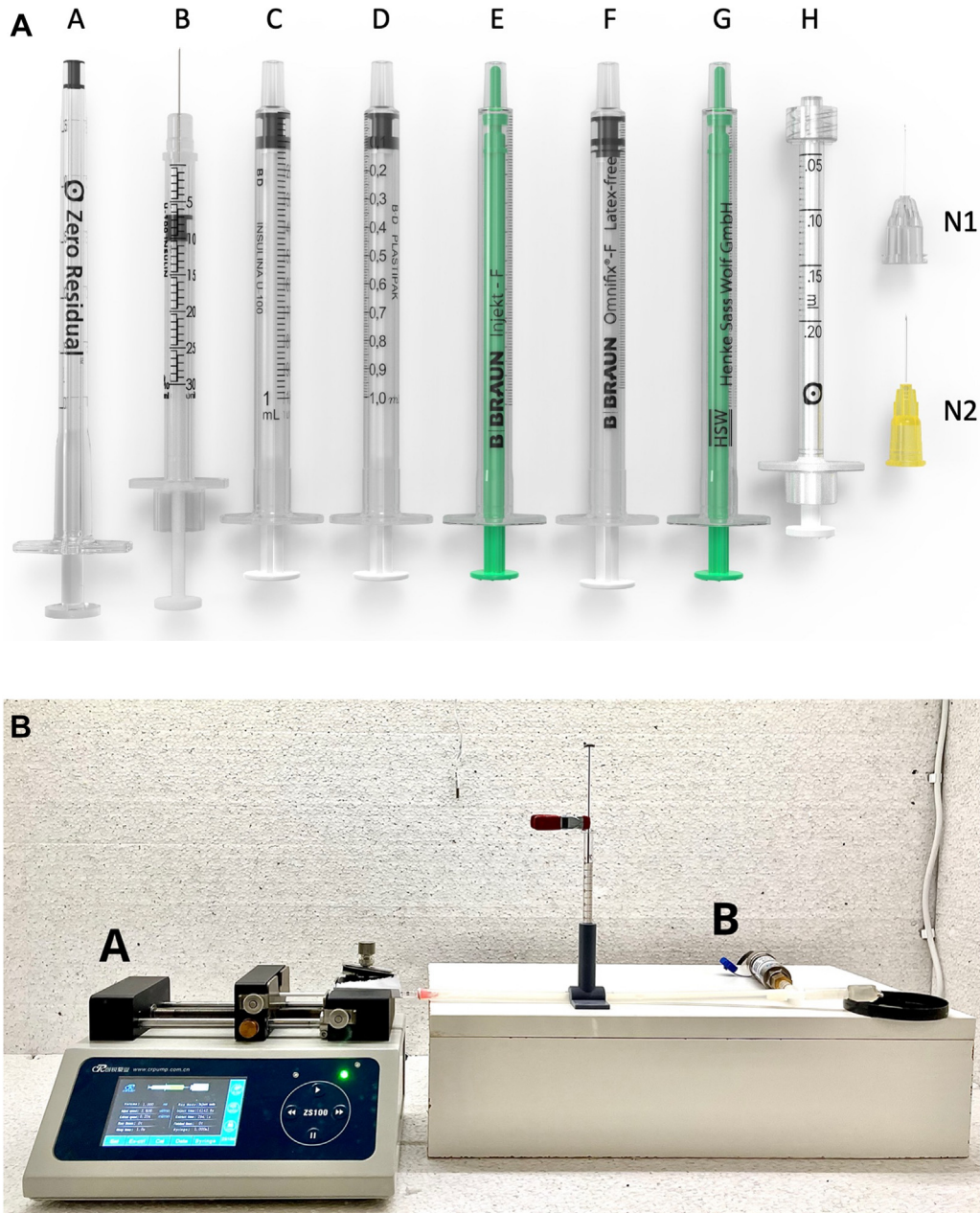


Figure 1. Syringes, needles and intraocular pressure experimental eye model. **A**, Illustrative images of the syringes and needles included in the study: A, Zero Residual 0.3 ml; B, Becton Dickinson (BD) Ultra-Fine 0.3 ml; C, BD Plastipak Brazil 1 mL; D, BD Plastipak Spain 1 ml; E, B. Braun Injekt-F 1 ml; F, B. Braun Omnifix-F 1 ml; G, HSW Norm-Ject 1 ml; and H, Zero Residual Silicone Oil-free 0.2 ml; N1, 34-gauge TSK The Invisible Needle; N2, 30-gauge Zero Residual Needle. **B**, Setup for the fluid dynamics experiments. A high-precision syringe pump (A) houses a syringe filled with distilled water. The syringe attaches to a tube plugged with a rubber stopper with 2 needles. The needle dimensions produce a steady-state pressure of about 15 mmHg at physiologic flow rate of 2.5 μ L/min. A dynamic pressure transducer (B) measures the upstream pressure after injection of incrementally increasing volumes of distilled water into the system. As the viscosity of water is temperature-dependent, we performed the experiments in a polystyrene container heated to 30° C.

only until recently that a study showed that a substantial proportion of IVIs in clinical practice indeed miss the 0.05-ml target volume.^{7,8} An underlying explanation was the poor accuracy of the syringes used in the clinical study, potentially exaggerating the IOP elevation because of IVI of higher-than-anticipated volumes. Inevitably, the same syringes also contained a risk of dispensing lower-than-anticipated volumes, potentially diminishing the therapeutic effect of anti-VEGF, and the authors highlighted the need for a syringe specifically designed for IVI.

A clear economic impact can also be seen with reduced syringe accuracy. Overdelivery implicates drug wastage, whereas underdelivery implicates less effective treatment, demanding more injections for a treatment modality already known to be long-lasting and expensive.^{11,12} Therefore, the aim of this study was to compare the accuracy and residual volume of commonly used syringes for IVI and to assess the IOP rise by variations in volumes delivered.

Methods

Accuracy, Precision, and Residual Volume Assessment

Syringes, Needles, and Fluids. We investigated 8 commercially available syringes with different designs (Fig 1A): Becton Dickinson (BD) Ultra-Fine 0.3 ml Short Needle with a half-unit scale (Becton Dickinson and Co), BD Plastipak 1 ml luer slip (Becton Dickinson S.A.), BD Plastipak 1 ml luer slip (Becton Dickinson S.A.), Braun Injekt-F 1 ml (B. Braun Medical Inc), Braun Omnifix-F 1 ml (B. Braun Medical Inc), HSW Norm-Ject Tuberculin (Henke Sass Wolf), Zero Residual 0.3 ml (SJJ Solutions BV), and Zero Residual Silicone Oil-free 0.2 ml syringe (SJJ Solutions BV) designed specifically for IVI. As for the needles, we used 2 commercially available models: 34-gauge TSK The Invisible needle (TSK Laboratory) or 30-gauge Zero Residual needle (SJJ Solutions BV). The BD Ultra-Fine 0.3-ml syringe has its own staked-in needle. All syringes and needles were from their respective same lots. Due to the nature of the study, institutional review board approval was not required. All research adhered to the tenets of the Declaration of Helsinki.

Because fluid density could influence the results, we performed all measurements with distilled water and glycerin solution under different conditions. We assessed 2 different volumes: 50 and 70 μ L. The former represents the standard IVI target volume for most drugs, whereas the latter corresponds to the volume for the 8-mg aflibercept formulation and also to the potentially more challenging skills required to select an intermediary grading line for some syringe models.

Withdrawing and Injection Technique. We used a sample size of 10 units for each syringe model in each subset of experiments, making up 80 units for 7 of them, except for the BD Ultra-Fine, which was not tested with the 2 needles because it has its own staked-in one, making up 40 units for this model.

An experienced ophthalmologist (T.A.C.) who was familiar with the IVI technique assessed each syringe and needle setup. The syringe was filled with 50 or 70 μ L of distilled water or glycerin solution with the study needle priorly attached. Then, air bubbles were carefully removed. Afterward, the plunger was slowly pushed to expel the fluid into an Eppendorf tube. The weight of the syringe-needle setup was then measured using an analytic scale before and after liquid aspiration as well as after its ejection. For each simulation, a new syringe and needle were used.

The weight of the syringe-needle setup after fluid withdrawing, after subtracting the previously measured empty set weight, represents the residual volume in the dead space of both devices together. All measured volumes are reported in μ L, with a resolution of 0.1 μ L based on the readability of the analytic scale of 0.1 mg, according to the scale manufacturer handbook.

The balance used was the OHAUS Analytical 220 g 4 houses PR Series PR224 (Thermo Fischer Scientific Inc). The scale has 3 essential weighing modes, RS-232 connectivity for data transfer and storage, and internal calibration. It was properly balanced and calibrated before measurements. Room temperature and humidity (23° C and 70%, respectively) were monitored and kept stable over the course of the study period.

In summary, each syringe model was exposed to 8 situations (needles A and B, liquids A and B, and volumes A and B), except the BD Ultra-Fine, which has its own staked-in needle (liquids A and B and volumes A and B). For each situation, 10 brand new syringe-needle setups were employed and then discarded.

Experimental IOP Spike Model

To determine the transient rise in IOP after IVI of a given volume, we created an experimental eye model. Apart from some modifications, our setup resembled previously described fluid dynamics experiments (Fig 1B).^{13–15} We used a high-precision ZA100 syringe pump (Baoding Chuang Rui Precision Pump Co, Ltd) housing a syringe filled with distilled water. We attached the syringe to a silicone tube with 9-mm outer diameter, 5-mm inner diameter, and 25-cm length. The tube formed a system with 5-ml inner volume, corresponding to the volume of a normal anterior chamber plus vitreous.^{16,17} We plugged the distal end of the tube and placed 2 needles of 19.6-mm length and 51- μ m inner diameter through the tube plug. Because the viscosity of water is temperature-dependent and the temperature is approximately 30° C in the anterior segment, we placed the equipment in a heated polystyrene container and ensured that the water held a temperature of 30° C throughout the experiments.¹⁸ We also made sure that water was free of microbubbles by visual observation. According to the Hagen-Poiseuille equation and the electronic-hydraulic analogy of parallel resistors, these conditions result in a theoretical steady-state pressure of about 15 mmHg at a physiologic flow rate of 2.5 μ L/min.¹⁹ We measured the actual pressure with a GD4200 dynamic pressure transducer (ESI Technology Ltd).

We first confirmed that the setup was resistance-free without the rubber stopper and syringes attached; i.e., the pressure was 0 mmHg at 2.5 μ L/min flow rate. We defined steady-state pressure as <1 mmHg pressure variation at 2.5 μ L/min flow rate for 30 minutes. After the system had reached steady-state pressure, we measured the transient rise in pressure after injection of the following volumes of water into the system: 20, 30, 40, 50 (standard anti-VEGF volume), 60, 70, and 80 μ L. To administer these volumes accurately, an industry-standard Hamilton 700 Series Microliter syringe (Hamilton) was used. The experiment was repeated 3 times for each volume.

Statistical Analysis

For the accuracy/residual volume subset of the study, we present data as mean $\pm$ standard deviation (SD) as well as percentage of exceeding volume from the target. The coefficient of variation (SD divided by mean) was calculated. For the IOP assessments, we determined the mean and SD. We used 1-way analysis of variance with post hoc Bonferroni correction for multiple comparisons. Stata version 16 was used for all tests.

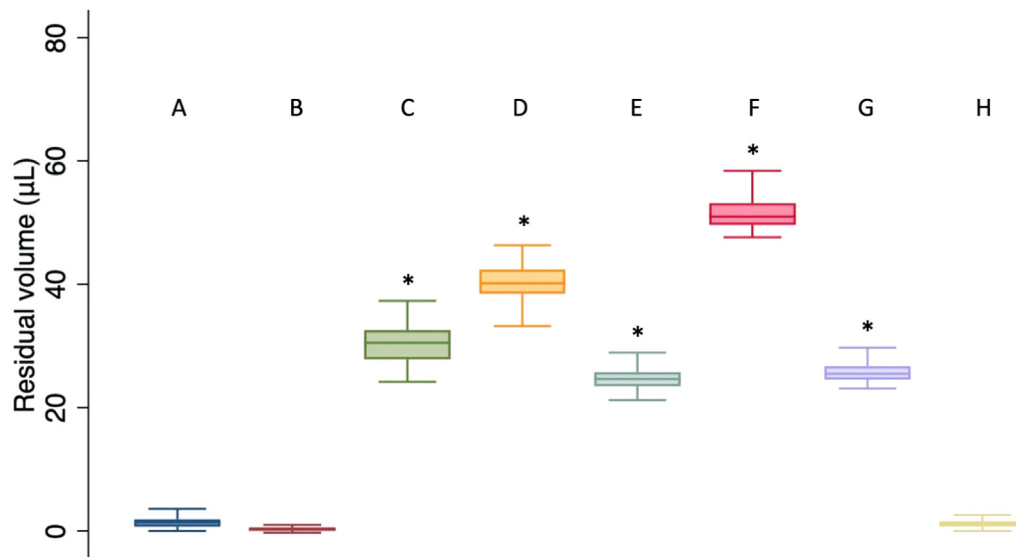


Figure 2. Residual volume for each syringe model when combining data for all subgroups. The Zero Residual Silicone Oil-free, the Zero Residual 0.3 ml, and the Becton Dickinson (BD) Ultra-Fine had the best performance. Syringes were labeled as: A, Zero Residual 0.3 ml; B, BD Ultra-Fine 0.3 ml; C, BD Plastipak Brazil 1 ml; D, BD Plastipak Spain 1 ml; E, B. Braun Injekt-F 1 ml; F, B. Braun Omnifix-F 1 ml; G, HSW Norm-Ject 1 ml; and H, Zero Residual Silicone Oil-free 0.2 ml. * $P < 0.001$ (compared with Zero Residual Silicone Oil-free; 1-way analysis of variance with post hoc Bonferroni correction for pairwise comparison).

Results

Accuracy, Precision, and Residual Volume Assessment

Among the 600 syringe-needle setups we tested, the BD Ultra-Fine ($0.34 \pm 0.28 \mu\text{L}$), the Zero Residual ($1.53 \pm 1.15 \mu\text{L}$) and the Zero Residual Silicone Oil-free 0.2-ml syringe ($1.40 \pm 1.16 \mu\text{L}$) had the lowest residual volume ($P < 0.0001$) in comparison with the others (range, $24.86 \pm 1.78 \mu\text{L}$ for the Injekt-F to $51.97 \pm 3.37 \mu\text{L}$ for Omnifix-F) when all subgroups (different volumes, fluid solutions, and needles) were analyzed together (Fig 2).

Table S1 (available at www.ophtalmologyretina.org) shows the descriptive data for the combined subgroups of each syringe model, only separated by the volumes of interest (50 and 70 μL). The coefficient of variation was $<10\%$ for most syringes, which implies they had a high precision.

Figure 3 shows the ejected volume for each setup. There was significant difference among the different syringes. The most accurate setup was the Zero Residual Silicone Oil-free 0.2-ml syringe, showing 0.70% volume excess. The other setups varied from 4.49% volume excess for Zero Residual 0.3 ml to 19.41% volume excess for BD Plastipak Spain. The results for the other setups were as follows: BD Ultra-Fine (7.83%), Injekt-F (9.42%), Norm-Ject (15.88%), Omnifix-F (16.96%), and BD Plastipak Brazil (17.96%) (see Figure 4). Pairwise comparisons showed a statistically significant difference between the Zero Residual Silicone Oil-free and the other syringes ($P < 0.0001$ for all comparisons), except for the Zero Residual 0.3-ml syringe ($P = 0.029$).

Experimental IOP Spike Model

We measured the steady-state pressure to be about 15 mmHg. Injection of a given volume of water into the system resulted in an

immediate rise in pressure followed by a hyperbolic decline in pressure, demonstrating outflow of a constant proportion of extra water per unit time (Fig 5). Increasing the injection volume resulted in increasing pressure rise and, to a lesser extent, increasing duration of the pressure rise.

The modeled IOP rise ranged from 32.3 (SD, 1.4) mmHg for 20- μL injection volume to 76.5 (SD, 1.0) mmHg for 80- μL injection volume. For the standard 50- μL injection volume, the peak pressure was 50.7 (SD, 0.1) mmHg, and the modeled pressure rise duration was 28 (SD, 2) minutes. Table 2 shows the peak pressure and the duration of pressure rise for all predefined injection volumes.

Discussion

Because IVI was established as an important route of administration for retinal ocular diseases, several methodologic aspects of this technique have been studied.^{20–24} Yet, only recently have the accuracy and precision of the devices used in these procedures become an increasing concern. It has been demonstrated that in most cases the dose effectively delivered to the eyes during IVI does not accurately constitute the intended dose, and these findings coincide with our results, that showed an important variation in accuracy and precision among the assessed syringes.^{25,26} The observation of the IOP fluctuation related to different volumes injected in our experimental eye model, in turn, seems to respond to the relevant question regarding how repeat IVI treatment and glaucoma might be interconnected.

The syringes and needles most commonly used for IVI in clinical practice are not developed for ophthalmic use. Recent studies have identified the following syringe characteristics that favor accuracy and precision: (1) a low volume with reduced smaller inner diameter and thus wider spacing marks;

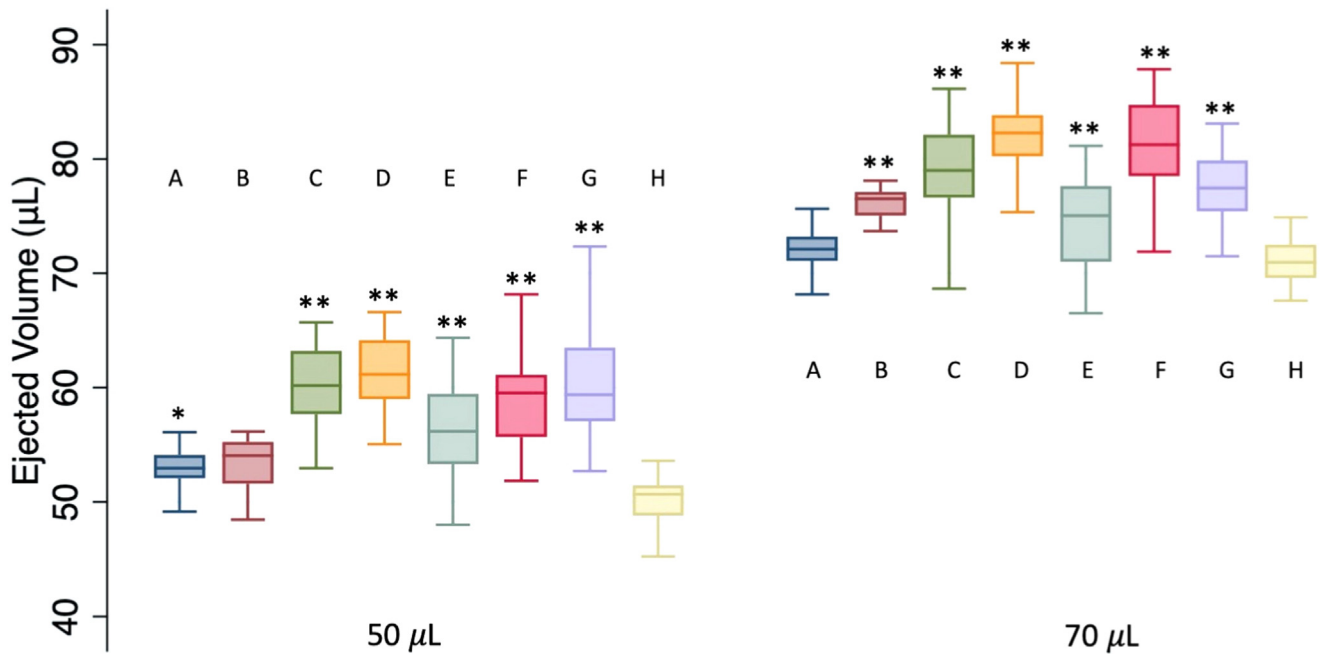


Figure 3. Ejected volume in μL for the 50- and 70- μL target volumes. The box-and-whiskers plot shows comparison between the intended and expelled volumes for each syringe model; the volume data set is presented separately for each volume group. Syringes were labeled as: A, Zero Residual 0.3 ml; B, Becton Dickinson (BD) Ultra-Fine 0.3 ml; C, BD Plastipak Brazil 1 ml; D, BD Plastipak Spain 1 ml; E, B. Braun Injekt-F 1 ml; F, B. Braun Omnifix-F 1 ml; G, HSW Norm-Ject 1 ml; and H, Zero Residual Silicone Oil-free 0.2 ml. * $P = 0.034$; ** $P < 0.0001$ (compared with Zero Residual Silicone Oil-free; 1-way analysis of variance with post hoc Bonferroni correction for pairwise comparison).

(2) a plunger designed to reduce the space between the inner wall of the syringe and the plunger itself to reduce the dead space; and (3) prefilling the syringe.^{4,24,27–29}

In this study, we assessed some of the most common syringe models used for IVI, including a new syringe designed for IVI of biologics.³⁰ In agreement with previous

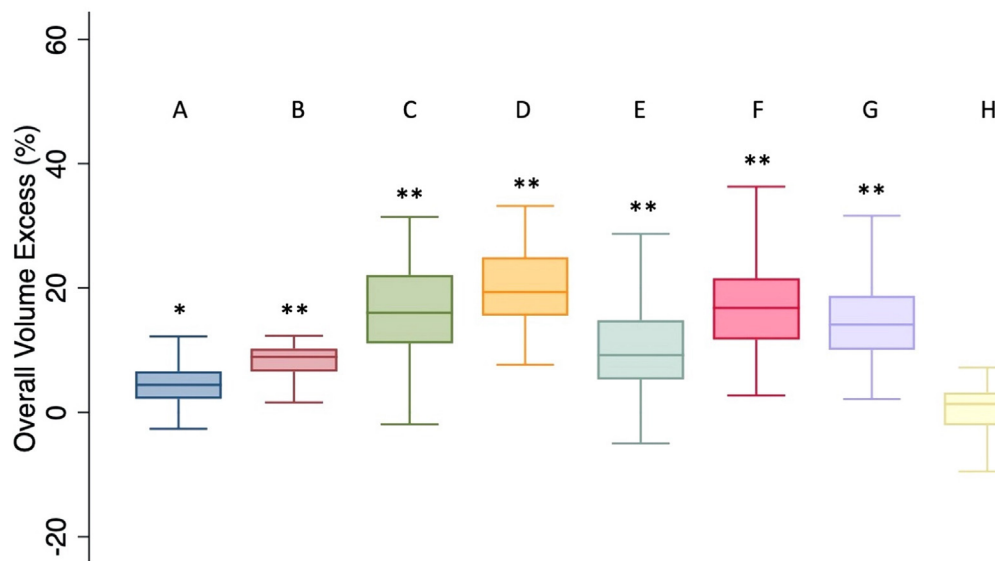


Figure 4. Overall volume excess in percentage considering all subgroups combined. The box-and-whiskers plot shows a significant overdelivery when all syringe-needle setups were compared with the Zero Residual Silicone Oil-free. Syringes were labeled as: A, Zero Residual 0.3 ml; B, Becton Dickinson (BD) Ultra-Fine 0.3 ml; C, BD Plastipak Brazil 1 ml; D, BD Plastipak Spain 1 ml; E, B. Braun Injekt-F 1 ml; F, B. Braun Omnifix-F 1 ml; G, HSW Norm-Ject 1 ml; and H, Zero Residual Silicone Oil-free 0.2 ml. * $P = 0.029$; ** $P = 0.000$ (compared with the Zero Residual Silicone Oil-free; 1-way analysis of variance with post hoc Bonferroni correction for pairwise comparison).

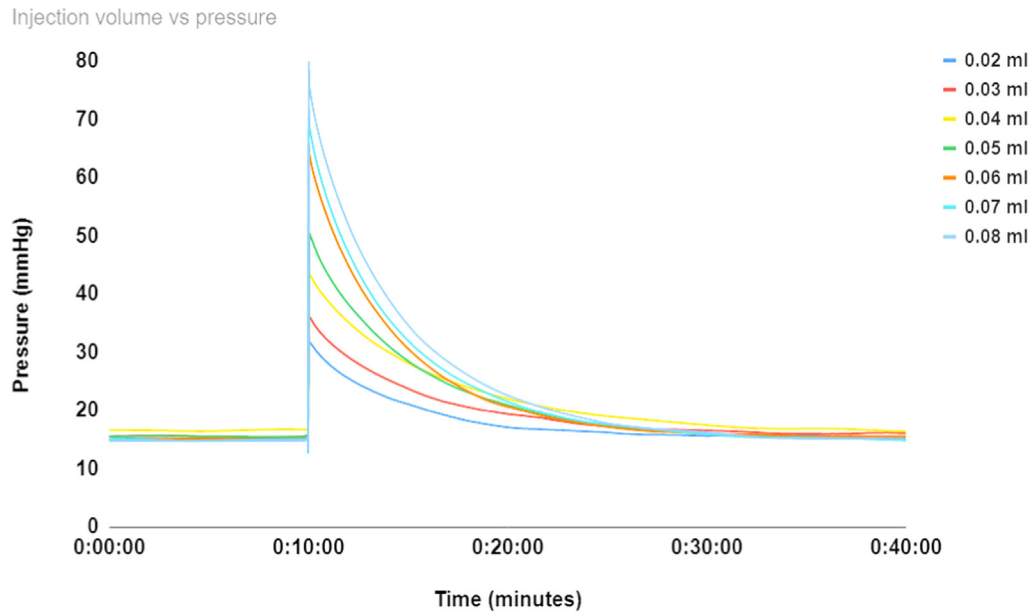


Figure 5. Printout of the dynamic pressure transducer display during injection of increasing volumes of water into the eye model. The steady-state pressure is approximately 15 mmHg. Each injection results in an immediate pressure rise, followed by a hyperbolic exponential decay in pressure; the steady-state pressure is again reached after about 30 minutes.

studies, our results showed a trend toward volume overdelivery, confirming poor accuracy and precision of most syringe-needle setups.

In our study, the BD Ultra-Fine syringe had low residual volume and a low tendency to overdeliver, which can be explained by small dead space because of its fixed needles.³¹ However, the potential of this syringe to release silicone oil has been reported in several articles, especially when agitated by flicking.^{32–34} The BD Ultra-Fine manufacturer also issued a security statement in January 2021, emphasizing that their syringes were not validated for IVI.³⁵

Both BD Plastipak models made in Brazil and Spain and Omnifix-F had higher rates of residual volume and overdelivery. The Injekt-F and HSW Norm-Ject also showed a high residual volume and overdelivery, despite having plungers designed to reduce dead space and, consequently, residual volume. A possible explanation is given by Havuz et al (2020); after testing 5 different injectors, they claimed that the difference in the design of low-dead space plungers might affect the administered volume, because lowering the potential space between the plunger and the needle may also lower the dead space.²⁷

In accordance with its design for handling small volumes, the Zero Residual syringes, and especially the Zero Residual Silicone Oil-free 0.2-ml syringe, had very low-residual volume and the lowest overdelivery among the tested models. Additionally, as its name implies, the Zero Residual Silicone Oil-free 0.2-ml syringe is silicone oil-free, abolishing the risk of silicone oil deposits in the vitreous in connection with the IVI procedure³⁶ (*Invest. Ophthalmol Vis Sci.* 56:1495, 2015). We proposed to evaluate 2 different fluids, considering the difference in density between the various liquids. Because anti-VEGF medications have a high concentration of proteins, it makes them more prone to inaccurate dosing because of bubble formation.⁴ Still, we did not find a statistically significant difference between water and glycerin-solution measurements, contradicting a previous report (*Invest. Ophthalmol Vis Sci.* 56:1495, 2015). A possible explanation is that the density of the glycerin solution is not as high as the density of anti-VEGF drugs, resulting in less bubble formation.

Another aspect we evaluated was whether the chosen injection volume affected accuracy and precision. Given the fact that the marks on some syringe models (BD Plastipak

Table 2. Peak Pressure and Duration of Pressure Rise after Injection of Increasing Volumes of Distilled Water into the Eye Model

	Injection Volume 20 μ L	Injection Volume 30 μ L	Injection Volume 40 μ L	Injection Volume 50 μ L	Injection Volume 60 μ L	Injection Volume 70 μ L	Injection Volume 80 μ L
Peak pressure, mmHg, mean (SD)	32.3 (1.4)	36.5 (2.7)	43.5 (0.4)	50.7 (0.1)	65.4 (4.3)	70.5 (1.8)	76.5 (1.0)
Duration of pressure rise, minutes, mean (SD)	25 (3)	28 (5)	33 (3)	28 (2)	27 (2)	34 (2)	33 (1)

SD = standard deviation.

Brazil, for instance) have an increment of 20 μ l and that the administered dose typically is 50 μ l (standard dose) or 70 μ l (as of aflibercept 8 mg), we hypothesized that the tested doses could induce more errors. However, our results did not show a difference between 50 and 70 μ l, suggesting that the inaccurate dosing is more related to other factors, such as plunger design or syringe volume.

Notably, accuracy measures how well a syringe delivers the intended volume consistently. A syringe with high accuracy will yield measurements that are close to the target volume. Precision, on the other hand, reflects the degree of variability among multiple measurements of the same quantity. It indicates how closely repeated measurements of the same volume agree with each other. A syringe with high precision will yield measurements that are close to each other.³⁷ In summary, a syringe can be accurate, precise, both accurate and precise, or neither accurate nor precise. We found a remarkable variation in accuracy between the syringes in the study, but all of them were found to be precise.

Interestingly, in the experimental eye model, we found a direct correlation between increase in injection volume and peak pressure after the injection. Combining this observation with the documented trend for drug overdelivery for commonly used syringes for IVI, we hypothesize a correlation between repeated IVIs, increased IOP, and retinal nerve fiber layer loss.^{38–40}

The evaluation of all these factors shows that the low accuracy of the syringes used in ophthalmic practice raises not only a medical issue, given the possibility of increased side effects in cases of overdose, and the low therapeutic efficacy in cases of underdoses, but also an economic issue. The disposal of biologic agents is not a matter of lesser importance, while the exacerbation of chronic diseases, such

as glaucoma, brings a very high personal cost to the patient and extends a naturally serious public health problem.

The strength of the current study is that we analyzed a wide range of syringes frequently used for IVI, including a syringe specially designed for ophthalmic use. Some study limitations should also be noted. The IOP data were experimental and could be strengthened in an animal model. Another limitation is that the injection needles used in the present study are not the most commonly used for IVI in many countries. Also, we tested needles with low dead space because we wanted to focus on the syringes. Because most needles also have an important residual volume in their hub (Melo, unpublished data, 2023), our study may partly underestimate the drug loss in clinical practice. One should also bear in mind that individual variations in technique can lead to different outcomes. A recent publication showed that additional force exerted over the plunger might lead to a higher delivered volume.⁴¹ Although we sought to employ the best technique, even subtle differences in pressure could have had some impact on the total volume delivered. Finally, prefilled syringes, which are commonly available for aflibercept and ranibizumab injection, were not included in this set of experiments because they have been much studied elsewhere.⁴²

In conclusion, this study shows significant variations in accuracy and residual volume among syringes commonly used for IVI, whereas they showed a high precision. Our findings provide evidence for a potential increase in the risk of side effects, such as exaggerated IOP elevation and increased risk of IVI-associated retinal nerve fiber layer loss in patients with glaucoma, wastage of expensive medications in case of overdelivery, and reduced therapeutic effect in the case of underdelivery.

Footnotes and Disclosures

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Analysis and interpretation: Agra, Sverstad, Kristianslund, Petrovski, Maia, Moe, Jørstad, Melo

Obtained funding: Melo, Moe, Jørstad

Overall responsibility: Agra, Sverstad, Kristianslund, Petrovski, Moe, Jørstad, Melo

Abbreviations and Acronyms:

BD = Becton Dickinson; **IOP** = intraocular pressure; **IVI** = intravitreal injection; **SD** = standard deviation.

Keywords:

Accuracy, Anti-VEGF, Intraocular pressure, Intravitreal injection, Residual volume, Syringe.

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