# Increased Risk of Severe Rise in Intraocular Pressure after Intravitreous Injection of Aflibercept with Prefilled Syringes – the role of ejection volume

Vita Louisa Sophie Dingerkus[1,2,3], Gábor Márk Somfai[1,2,3], Stephan Kinzl[1,2,3], Florian Moritz Heussen[1,2,3], Matthias Dieter Becker[1,2,3,4]

[1]Werner H. Spross Foundation for the Advancement of Research and Teaching in Ophthalmology, Zurich, Switzerland,
[2]Center for Clinical Research and Quality Assurance, Triemli Hospital, Zurich, Switzerland [3]Department of Ophthalmology, Triemli Hospital, Zurich, Switzerland
[4]Department of Ophthalmology, University of Heidelberg, Heidelberg, Germany

## Background

Intravitreous injections (IVI) with prefilled syringes (PFS) are supposed to reduce procedure time and the risk of endophthalmitis. [1]
Postoperative rise in intraocular pressure (IOP) is suspected to lead to glaucomatous changes [2] and there are informal reports that IOP can increase greatly following injections by the aflibercept PFS.
In June 2020, following the introduction of the new aflibercept PFS in our clinic, we observed an unusual incidence of severe spikes in intraocular pressure (IOP), leading to short-term transient visual loss in five eyes of five patients that were reported to Swiss Medic, the Swiss agency for therapeutic products.
Four of the five patients had diabetic retinopathy with macular edema and one had wet age-related macular degeneration. All eyes have already been treated with intravitreous anti-VEGF therapy with aflibercept vials without any complications. Two of the five eyes had to undergo a paracenthesis as the IOP was above 60mmHg whereas in the remaining three eyes the symptoms and IOP rise normalized spontaneously.
The exact emptying volume of PFSs has been assessed earlier describing some differences. [3,4] The preoperative preparation of the PFS in our clinic is the task of the injecting physician. Although the entire staff involved in the injections had been trained prior to the introduction of the aflibercept PFS in our clinic, our hypothesis was that the design of the new PFS and the injection technique may result in inaccurate injection volumes. Therefore, our aim was to analyze the emptying volumes (EV) of the aflibercept PFS depending on the injection technique.

## Methods

The amount of the EV was assessed using 40 aflibercept PFS. We measured the EV in four different groups with 10 injections in each group: in the first two groups, the cone was set precisely at the indication line (Normal Volume, NV) and the fluid was ejected without (nP) or with forced pressure (wP) at the end of emptying the syringe (NVnP and NVwP, respectively). In two further groups, the plunger was set right below the line (High Volume, HV) and was ejected without or with forced pressure (HVnP and HVwP, respectively). (Figure 1.) A laboratory weighing scale (AX105 DeltaRange®, Mettler Toledo, Ohio) was used for the measurements of EV (calculated with a density of 1.034 mg/ml for aflibercept).
The volumes were compared with a Welch's ANOVA as variances were not equal. Normality was checked with a QQ-plot and Shapiro-Wilk normality test. Pairwise comparisons using t-tests with non-pooled standard deviation and Holm's p-value adjustment was also performed.

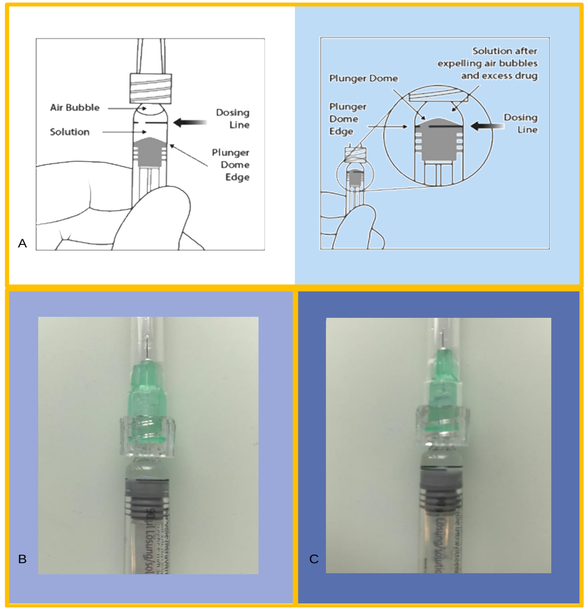


**Figure 1.** Injection technique with the Eylea PFS. A) Instructions for depressing the plunger rod to align the cylindrical base of the plunger dome edge with the black dosing line on the pre-filled syringe. Image is taken from the manufacturer`s guideline. B) Correct alignment of the plunger rod. C) Incorrect alignment with the cylindrical base slightly beneath the dosing line. In the every day routine, perfect alignment may not always be achieved.

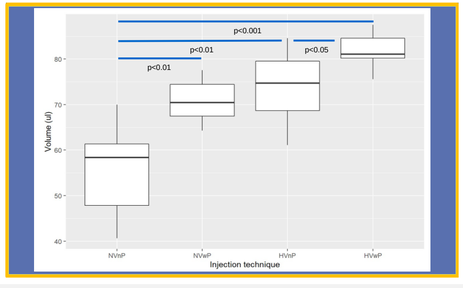


**Figure 2.** Boxplot of volume by injection technique. The line in the box stands for the median, the lower and upper hinges correspond to the first and third quartile. The four different groups are Nomal Volume without forced pressure (NVnP) or with forced pressure (NVwP) at the end of emptying the syringe , and High Volume without or with forced pressure (HVnP and HVwP groups). The p-values under the blue lines indicate the pairwise comparisons using t-tests with non-pooled standard deviations (SD). Note that SD are higher within the groups in which no forced pressure at the end of emptying the syringe was used indicating higher variability of EV.

## Results

The EV values in the NVnP, NVwP, HVnP and HVwP groups were 56.06 ± 10.32, 70.69 ± 4.56, 74.22 ± 7.41 and 81.63 ± 3.67 µl, respectively. (Figure 2.)
The results of Welch's ANOVA indicated that volumes were significantly different between the four injection techniques ($p<0.001$). Pairwise post-hoc tests showed that EVs in all four groups differed significantly from each other except for the comparison of NVwP and HVnP. The NVnP group had significantly lower EV compared to all other groups.
The EV in three cases (30%) was below 50 µl in the NVnP group (40.62, 42.35 and 45.64 µl) while in the NVwP group all values were above 64 µl, with 7 values (70%) exceeding 70 µl. In the HVwP group 8 measurements (80%) exceeded an EV of 80 µl.

## Conclusion

Our results point toward the importance of the right injection technique with the aflibercept PFS to ensure the correct amount of drug delivered intravitreally. Even with the right injection technique the drug can be underdosed in one third of the cases as deviations may likely to occur when, according to the recommendation, no forced pressure at the end of emptying the syringe is used.
On the other hand, 60% (30 µl) excess volume can be achieved by using suboptimal settings and a suboptimal injection technique, potentially leading to a rise in intraocular pressure postoperatively.
One explanation for the large variations seen in our study could be the design including the relatively high syringe diameter of the aflibercept PFS. This should be taken into consideration when applying it in the daily routine and might be addressed in future development of further PFS.
It needs to be noted that 100 µl injection volume, e.g. in the case of intravitreous triamcinolone, can be well tolerated without IOP rise. Therefore, our results could not clearly explain our clinical observations.

## References

1. Storey PP, Tauqeer Z, Yonekawa Y, et al., Am J Ophthalmol. 2019 Mar;199:200-208.
2. de Vries VA, Bassil FL, Ramdas WD, Sci Rep. 2020 Aug 6;10(1):13248.
3. Moisseiev E, Rudell J, Tieu EV, Yiu G, Curr Eye Res. 2017 Jul;42(7):1059-1063.
4. Loewenstein I, Goldstein M, Moisseiev J, et al, Retina. 2019 Jul;39(7):1385-1391.

Financial Disclosures:
VLSD (none), GMS (Allergan, Bayer, Novartis C), SK (Novartis C), FMH (none), MDB (Roche)

Email: vita.dingerkus@zuerich.ch