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CORRESPONDENCE

# Pre-filled aflibercept syringes—variability in expressed fluid volumes and a case series of transient central retinal artery occlusions

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## To the Editor:

Intravitreal aflibercept has been used in the UK for treatment of a variety of retinal vascular disorders and from April 2020 has had market authorisation for use in a pre-filled syringe (PFS).

We report a series of five eyes in four patients who developed transient CRAO immediately post injection using the PFS (see Table 1). These occurred shortly after the adoption of the PFS in our departments. All patients had previously received intravitreal injections (ranibizumab or aflibercept) without complication.

Following these events, we investigated the volume of fluid expressed when using a standard 1 ml syringe compared to the new aflibercept PFS.

Six injectors drew water into an empty aflibercept PFS and a standard 1 ml syringe, primed them to 0.05 ml and then expressed the contents into a receptacle on a weighing scale (Hooiswee, Shenzen, China). The mass of water was recorded (0.05 ml having a mass of 0.05 g. Results reported as volumes in ml). This was repeated 20 times for each syringe (Total of 120 repeats for each syringe). Data were analysed with MS Excel with StatPlus.

Epoxy resin casts were taken of each syringe and Vernier callipers used to measure the internal diameter.

The mean volume of water expelled per repeat was 0.063 ml (SD 0.009 ml) for the PFS and 0.054 ml (SD 0.002 ml) for the 1 ml syringe (difference 0.009 ml, $p = 8.3 \times 10^{-20}$, 95% CI 0.007–0.011) (see Fig. 1). The maximum volume expressed was 0.064 ml for the 1 ml syringe and 0.084 ml for the PFS.

The PFS expressed a greater range of volumes than the 1 ml syringe with 21% of PFS repeats expressing 0.07 ml or more.

### Changes in volume with errors in syringe plunger position

The measured internal diameter was 6.4 mm for the PFS and 4.6 mm for the 1 ml syringe. (For comparison, the internal diameter of the ranibizumab PFS was also measured as 4.6 mm). Therefore, the calculated internal area ($\pi r^2$) was 32 $mm^2$ for the aflibercept PFS and 16.6 $mm^2$ for the 1 ml syringe.

Any error in alignment with the 0.05 ml mark will result in an error in the volume expressed. The size of this error is determined by the linear error in plunger alignment multiplied by the internal area of the syringe.

Thus, any unit error in plunger alignment will result in approximately a twofold greater error in volume for the PFS as compared to the 1 ml syringe.

Pallikaris et al. [1] demonstrated a linear relationship between IOP rise and volume injected. For the majority of patients, the observed errors in volume are unlikely to have any clinically significant impact. The risk of transient CRAO, even with higher injected volumes is still low [2]. There will be a subset of patients however for whom these higher volumes may be more significant (e.g. advanced glaucoma, low ocular perfusion pressure). Given that the wider diameter syringe results in a doubling of the volume error with each unit error in plunger alignment, it is particularly important with the

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**Table 1** Case series of patients developing transient CRAO after intravitreal injection with a pre-filled aflibercept syringe.

| Case | Age | Gender | Diagnosis | PMH | Side | POH/case description |
|---|---|---|---|---|---|---|
| 1 | 83 | F | AMD | • Depression<br>• Osteoporosis | Left | Six previous ranibizumab injections (in 2018) left eye without complication.<br>Disease reactivated 2020—first aflibercept of new course of treatment (pre-filled syringe) with CRAO immediately after injection. CRAO resolved after paracentesis. |
| 2 | 81 | M | AMD | • Ischaemic heart disease | Left | Ten previous aflibercept injections (from vial) without complication. Left aflibercept number 11 with pre-filled syringe with CRAO immediately after injection. CRAO resolved after paracentesis. |
| 3 | 78 | F | AMD | • Migraine<br>• Stroke 20 years ago<br>• Hypertension<br>• Hypercholesterolaemia<br>• Hypothyroidism | Bilateral | Previous ranibizumab injections (right × 7, left × 5). Aflibercept (from vial) both eyes × 1 without complication.<br>Patient then received bilateral aflibercept injections with pre-filled syringe. Developed CRAO immediately after right injection. Resolved after paracentesis.<br>Left IOP measured pre-injection as 14 mmHg and given G. apraclonidine 1% pre-injection. Left aflibercept injection given and patient developed CRAO in left eye also. Also resolved after paracentesis. |
| 4 | 37 | F | DMO | • Diabetes mellitus | Left | Three previous aflibercept injections (from vial) without complication. Immediately post injection using the pre-filled syringe, vision NPL with associated ocular pain. IOP 69 mmHg. Given G apraclonidine 1% and acetazolamide. After 7 min, pain easing, IOP 50 mmHg and perfusion present in CRA. Paracentesis was prepared but not performed as perfusion present. IOP continued to fall over next 20 min and vision returned to normal by 30 min. |

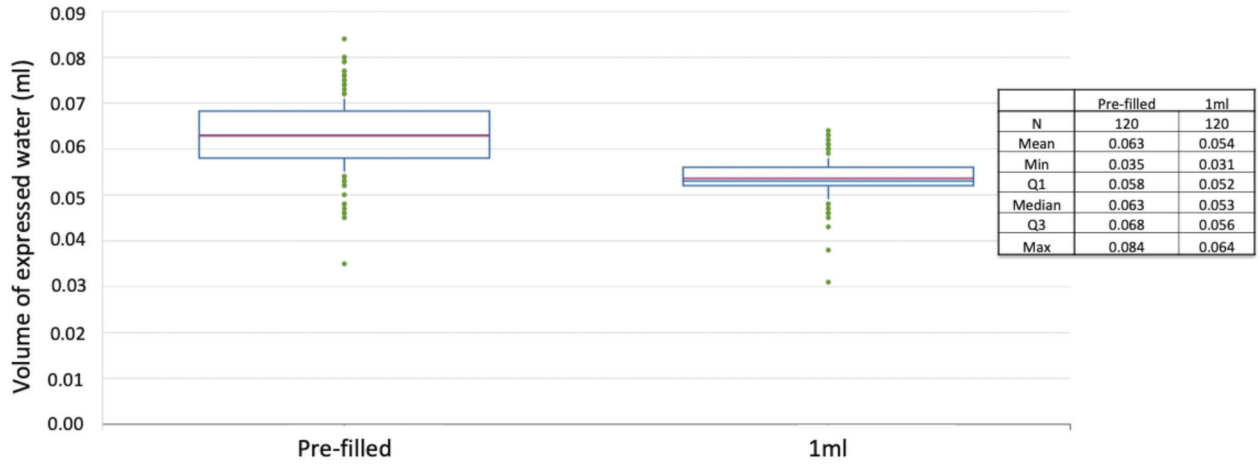


**Fig. 1 Box plot showing greater variability of expressed volumes with PFS vs 1 ml syringe.** Box plot comparing pre-filled aflibercept syringe with standard 1 ml syringe.

aflibercept PFS to pay close attention to the plunger position.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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