Title: To Analyze the dead space syringe for intra-vitreous injections

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Short title: dead space syringe injections

Abstract

Introduction: The introduction of antibody-based biologics targeting of the vascular endothelial growth factor (VEGF) to treat retinal diseases changed the approach for maculopathies. The injections are highly effective and have markedly decreased the risk of visual impairment. Since this kind of diseases are chronic in their nature, and most patients need long-term therapy to suppress disease activity the necessity to reduce the waste has to be considered. Many countries developed methods to compound in multiples doses the anti-VEGF without compromising drug stability or activity.

Objective: We evaluated the residual syringe volume waste sed for anti-VEGF injections in the Brazilian market.

Methods: Eight different models of plastic syringes were evaluated to analyze the residual volume after injections. Each syringe model was divided in groups with 10 samples and each sample was measured the weight using a caliper: before fill the volume, after fill the volume of 0.05ml and after the injection. We compared results to evaluate the syringe with low residual waste volume.

Results: The means residual volume of the group were between 0.002g to 0.032g. The syringe without needle had the higher weight with a statistic significant results in comparison with all the syringes with permanent needle. There were no statistic significant residual volume in all syringes with permanent needle.

Conclusion: We highly incentive physicians to use syringe with permanent needle to perform intra-vitreous injections.

Ranibizumab (Genentech, San Francisco, CA, USA) and aflibercept (Regeneron, Tarrytown, N.Y., and Bayer Health care, Leverkusen, Germany) are the anti-VEGF drugs widely used for the treatment of many exudative and neovascular retinal diseases of the eye, they have been approved for ophthalmological use by national and multinational drug agencies. Each patient received monthly injection of 0.05ml of the drug at least for 6 months during one-year period of treatment1. The commercial presentation of ranibizumab and aflibercept are 3 ml glass vial with a chlorobutyl rubber stopper containing 0.23 ml of ranibizumab2 and 0,278 ml of aflibercept3; the procedure requires withdraw all the fluid volume from the vial into an insulin syringe using an 18-gauge filter needle, despising the extra volume to reach 0,05ml and then preform the injection using an 30-gauge needle. A great amount of drug volume is sequestered at the dead spaces of both syringe and needle hubs.

The introduction of the injections as the standard of care in several ophthalmology conditions has placed a heavy economic burden on health care systems leadings. Some countries using the pharmacologic economic to split the drug into several syringes demonstrated a large impact on costs. In this context, a standardized, quality-controlled, time- and cost- efficient injection practice is paramount, and any means of improving either efficiency or safety is invaluable4.

In this study, we described a novel method to quantify the waste volume left into the plastic syringe after anti-VEGF injection and elected the best plastic syringe to use during intra-vitreous injections.

Material and Methods

We evaluated the amount of fluid retained in eight different types of insulin/tuberculin syringes with permanent needle design and without needle design (BD - Becton Dickinson & Co., Franklin Lakes, NJ, USA) used to perform intra-vitreous injections of anti-VEGF commercially available in the Brazilian marketing (table 1). Firstly, we divided the syringes types in group of ten samples and they all were weighted using a precise (0.01g) caliper balance (Ohaus Corp. Parsipanny, NY, USA).

In a second phase we filled the syringes with water, removed air bubbles and then pushed the syringe piston to the mark of 0,05ml. All the syringes were immediately weighted again. Then, we simulated an intra-vitreous injection pushing the piston to the end (mark 0.00) and we immediately weighted. In summary, we weighted the syringes before, within water and after simulation the injection to evaluate the residual waste volume of each type of syringe.

Statistical analyses were performed using the t-test and a p-value less than 0.05 was considered a statistically significant result.

Results

All results are described in the table 2 and 3. Mean residual weight into the dead space of syringes with permanent needle design was between 0.002 to 0.006 g and the syringe without needle was 0.032g. No statistic significant was observed in samples of syringe with permanent needle design but comparing all syringes with permanent needle design to the syringe without needle all results were statistically significant (P < 0.01). This indicates that a significant amount of volume loss is due to dead space if we use syringe without needle design.

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| Table 1. Syringe branch, model and image |
| Syringe type | Image |
| BD ultra fine II 0.5ml within 30g needle (8mm x 0.3mm) | Resultado de imagem para seringa BD ultra fine |
| BD ultra fine 0.5ml within 31g needle (6mm x 0.25mm) | Resultado de imagem para seringa BD ultra fine |
| BD ultra fine II 1ml within 31gneedle (8mm x 0.3mm) | Resultado de imagem para seringa BD ultra fine |
| BD ultra fine 1ml within 31g needle (6mm x 0.25mm) | Resultado de imagem para seringa BD ultra fine |
| BD ultra fine II 0.3ml 31g within needle (8mm x 0.3mm) | Resultado de imagem para seringa BD ultra fine |
| BD ultra fine 0.3ml 31g within needle (6mm x 0.25mm) | Resultado de imagem para seringa BD ultra fine |
| BD Plastic 1ml without needle |  Resultado de imagem para seringa BD platic 1ml |

\*BD - Becton Dickinson & Co., Franklin Lakes, NJ

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| Table 2. Syringe branch/model, residual weight (g), max residual volume (g), Minimum residual volume (g) and Standard deviation |
| Syringe type | Residual weight | Max | Minimum | SD |
| BD ultra fine II 0.5ml within 30g needle (8mm x 0.3mm) | 0.002 | 0.01 | 0.00 | 0.004 |
| BD ultra fine 0.5ml within 31g needle (6mm x 0.25mm) | 0.003 | 0.01 | 0.00 | 0.005 |
| BD ultra fine II 1ml within 31gneedle (8mm x 0.3mm) | 0.003 | 0.02 | 0.00 | 0.007 |
| BD ultra fine 1ml within 31g needle (6mm x 0.25mm) | 0.004 | 0.01 | 0.00 | 0.005 |
| BD ultra fine II 0.3ml 31g within needle (8mm x 0.3mm) | 0.005 | 0.02 | 0.00 | 0.007 |
| BD ultra fine 0.3ml 31g within needle (6mm x 0.25mm) | 0.006 | 0.02 | 0.00 | 0.007 |
| BD Plastic 1ml without needle | 0.032 | 0.05 | 0.02 | 0.010 |

\*BD - Becton Dickinson & Co., Franklin Lakes, NJ

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| Table 3. Syringe branch/model, weight of the recommended dose (g) and residual weight after injection (g) |
| Syringe type | dose | Residual weigh |
| BD ultra fine II 0.5ml within 30g needle (8mm x 0.3mm) | 0.055 | 0.002 |
| BD ultra fine 0.5ml within 31g needle (6mm x 0.25mm) | 0.052 | 0.003 |
| BD ultra fine II 1ml within 31gneedle (8mm x 0.3mm) | 0.053 | 0.003 |
| BD ultra fine 1ml within 31g needle (6mm x 0.25mm) | 0.049 | 0.004 |
| BD ultra fine II 0.3ml 31g within needle (8mm x 0.3mm) | 0.050 | 0.005 |
| BD ultra fine 0.3ml 31g within needle (6mm x 0.25mm) | 0.048 | 0.006 |
| BD Plastic 1ml without needle | 0.054 | 0.032 |

\*BD - Becton Dickinson & Co., Franklin Lakes, NJ

Discussion

A syringe to minimal drug waste for intra-vitreous injection of anti-VEGF is necessary to reduce the treatment cost of the patients due to the increased number of the injections per year5,6,7,8 . Souza et al demonstrated in patients that using syringe without needle took a 0.05ml residual volume of insulin after injections9. Ribeiro et al developed a technic to reduce the residual volume left in the complex needle-syringe in approximately 0.09ml10. Although these two studies have been performed using syringes without needle, our study suggests the use of syringes with permanent needle may reduce significantly the waste volume.

New cases of retinal disease are identified each year and the regulatory governments affairs are approving the use of the anti-VEGF as a new treatment (e.g. diabetic or vein occlusion macular edema, diabetic retinopathy and wet AMD) will increase more and more. the number of injections consequently increase the waste of the drug realistic and the drug fractioning is a reality. Hillingworth et. al. demonstrated in his paper an increase of 215% in injections procedure between 2010/2011 and 2014/15 in England Hospitals5.

Our study showed if we use a syringe without needle a residual volume of 58 per cent of the total amount injected remains in dead space, which means a despise of one dose treatment (0.05ml) for each two injections . During the years of 2006 to 2015 almost one billion injections were performed8 in USA. Considering the use of syringe with permanent needle we should save almost half treatment dose per injection and consequently reducing the cost treatment.

Recently the pre-filled syringe system with billed rubber stopper was lunched in the intentions of reduce significant amount of drug loss due to dead space volume11,12 but the syringes design does not come with permanent needle and the volume of the drug is more than one dose per syringe, that means at least a waste of one extra dose/treatment per injection. Cao et al demonstrated that ranibizumab and aflibercept can be effectively compounded into multiple doses of 0.05ml and stored for 4 weeks without lose treatment properties and suggests that compounds do not affect in vitro functional activity after up to 4 weeks of storage, thereby potentially reducing cost treatment for patients13. It is a time for challenging the biotechnology companies and regulatory government affairs to understand the necessity to decrease the price of the injections by reducing the volume of the anti-VEGF syringes with permanent needle. However this topic is not the main purpose of this paper.

In conclusion, we highly incentive physicians to use syringe with permanent needle to perform intra-vitreous injections. New techniques to compounder into multiple doses the anti-VEGF using syringes with permanent needle is necessary to reduce the treatment cost per patient.

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