Identifying risk factors for silicone oil droplets in anti-VEGF injections: a quantitative in vitro study

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ALLERGAN
Summary

- **Intravitreal injections:**
  - Silicone oil (SiO) droplets are released by syringes

- **Purpose:**
  - To examine potential risk factors of release of silicone oil droplets in anti-VEGF injections

- **Methods:**
  - Quantitative in-vitro study
  - Study the source of silicone oil droplets: compounding, delivery syringe
  - Impact on the quantity of SiO: technique, drug
Summary

Conclusions:
- Compounding processes can be a source of SiO droplets
- Variability between the 3 anti-VEGF agents
- Variability between insulin syringes
Introduction

- Silicone oil (SiO) droplets are released by syringes and found in the vitreous of patients that received intra-vitreal injections (Bakri and Ekdawi, 2008; Freund et al., 2006).

- These droplets can lead to:
  - Complaint of floaters that, in some cases, require vitrectomy (Hahn et al., 2015)
  - Post injection glaucoma: clogging of the trabecular meshwork (Wingard, et al., 2019)
Purpose

- To examine some potential risk factors of release of silicone oil droplets in anti-VEGF injections
  - compounding
  - injection techniques
  - drug
Methods

- Quantitative in-vitro study
- Three anti-VEGF agents (Bevacizumab, Ranibizumab and Aflibercept) + control (sterile water for injection)
- Compounding process:
  - the content of the industry vials was drawn into a 3 ml syringe ("base syringe" – BD and TERUMO)
  - compounded into the drug delivery syringe (BD 0.3ml Insulin Syringe).
Methods

- The contents were injected into amber glass vials (silicone-free)

- Four different techniques of injections:
  - Normal
  - Heavy
  - Agitation
  - Overfill
Methods: techniques

Normal:

Heavy:

Agitation:

Overfill:

• Syringe prepared with .07 ml
• .02 ml is primed
• .05 ml is injected
Methods

- Content was examined for the presence and quantity of SiO droplets

- 100 x magnification with a Brightfield light microscope

- Hand tally counter was used to count the number of drops.

- Each vial was tested in triplicate (3x3µL)
Methods
Rationale/Hypothesis

- **Source of silicone oil droplets:**
  - Base syringe (compounding)?
    - OR
  - Delivery syringe?

- **Impact on the presence:**
  - Technique?
    - OR
  - Drug?
Results

Organization of trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total of Trials:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept</td>
<td>228</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>246</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>108</td>
</tr>
<tr>
<td>Control</td>
<td>246</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>828</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Syringe</th>
<th>Total of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery syringe (after compounding)</td>
<td>792</td>
</tr>
<tr>
<td>Base syringe only</td>
<td>36</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>828</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technique</th>
<th>Total of Trials:</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>288</td>
</tr>
<tr>
<td>heavy</td>
<td>288</td>
</tr>
<tr>
<td>overfill</td>
<td>108</td>
</tr>
<tr>
<td>agitation</td>
<td>108</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>828</strong></td>
</tr>
</tbody>
</table>
Results

- Base syringe (3cc) for compounding:
  - TERUMO VS BD
  - By student’s t-test, there was no significant difference in the quantity of SiO oil found, p=0.376

-> TEST FOR SiO Droplets
Results

Base syringe & Delivery syringe:

TERUMO VS BD

By Student’s T test, there was a statistically significant difference between the quantity of SiO droplets between BD and Terumo base syringes, p=0.05
Results

Technique

Heavy vs normal vs agitation vs overfill

One way ANOVA: there was no significant difference in quantity of SiO found between groups, $p > 0.05$ ($p = .189$);
Results

Drug

Aflibercept vs Bevacizumab vs Ranibizumab vs Control (Water)

SiO drops/ trial (Mean)

Conducted one-way ANOVA comparing quantity of SiO droplets (significant)
Compounding processes can be a source of SiO droplets for anti-VEGF injections.
Conclusion

- Syringes containing anti-VEGF agents release more silicone oil droplets compared to syringes with control (water).
  - Suggesting a possible interaction between the anti-VEGF molecules and SiO.
  - Different between the 3 anti-VEGF agents studied.

<table>
<thead>
<tr>
<th></th>
<th>SiO drops/trial (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept (N=228)</td>
<td>5.87</td>
</tr>
<tr>
<td>Bevacizumab (N=246)</td>
<td>3.24</td>
</tr>
<tr>
<td>Ranibizumab (N=108)</td>
<td>0.82</td>
</tr>
<tr>
<td>Water (N=246)</td>
<td>0.41</td>
</tr>
</tbody>
</table>
The “Heavy force” technique is associated with an increased number of SiO droplets per trial.

Not statistically significant
Conclusion

- This study has also showed variability between insulin syringes of the same manufacturer
- suggesting that the amount of SiO as lubricant in each syringe may be variable.

<table>
<thead>
<tr>
<th>Technique</th>
<th>drops of SiO/ trial</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>Maximum</td>
<td>Minimum</td>
</tr>
<tr>
<td>Normal</td>
<td>288</td>
<td>2.31</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Heavy</td>
<td>288</td>
<td>3.95</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Overfill</td>
<td>108</td>
<td>2.65</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Agitation</td>
<td>108</td>
<td>2.09</td>
<td>27</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average SiO drops/trial (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept (N=228)</td>
<td>5.87 (0-50)</td>
</tr>
<tr>
<td>Bevacizumab (N=246)</td>
<td>3.24 (0-50)</td>
</tr>
<tr>
<td>Ranibizumab (N=108)</td>
<td>.82 (0-9)</td>
</tr>
<tr>
<td>Water (N=246)</td>
<td>.41 (0-17)</td>
</tr>
</tbody>
</table>
Thank you