Complications of Cosmetic Botulinum Toxin A Injections to the Upper Face: A Systematic Review and Meta-Analysis

David Zargaran, F Zoller, A Zargaran, E Rahman, A Woollard, Tim Weyrich, Afshin Mosahebi
background

- global increase in use of anti-aging products
- BoNT-A injections increasing due to relatively low price and perceived minimal downtime
- regulations are limited both nationally and internationally
- increasing concern in safety profile due to unregulated nature of administration
• identify the overall complication rate of cosmetic BoNT-A across randomized controlled trials, thereby helping establish the safety profile of BoNT-A
methods
systematic review
inclusion criteria

- in-vivo studies
- English language
- Adult humans over 18 years
- Papers published prior to 1989 were excluded
- Randomized placebo-controlled trials
- Cosmetic facial BoNT-A injection in the glabellar or forehead region
- At least 1 complication reported
complications

confounders
1. localized skin reaction (erythema, eczema, hematoma, bruising, or contusion)
2. remote skin reactions (rash or edema)
3. wound infection
4. asymmetric or unsatisfying result;
5. facial neuromuscular symptoms (stiffness, weakness, pain, spasm, paresis, ptosis, dysesthesia)
6. headache
7. ocular symptoms and infections
8. pulmonary symptoms and infections
9. gastrointestinal symptoms
10. cardiovascular symptoms (hypertension, hypotension, tachycardia, myocardial infarction)
11. general symptoms (influenza-like symptoms, asthenia, chills, pyrexia, fatigue)
12. anaphylactic reaction
13. others
data extraction

practitioners were categorized as doctor, nurse, or non-medical professional

BoNT-A formulations were onabotulinum (ONA), abobotulinum (ABO), and incobotulinum (INCO)

doses were categorized as 0 to 10 U, 11 to 20 U, 21 to 30 U, 31 to 40 U, 41 to 50 U, and 50+ U.

quality assessment tool: Effective Public Healthcare Panacea Project
results
Study | Cases | Total | Proportion | 95%-CI | Weight
--- | --- | --- | --- | --- | ---
Ascher et al. 2004 | 7 | 102 | 0.07 | [0.03; 0.14] | 5.1%
Ascher et al. 2005 | 7 | 50 | 0.14 | [0.06; 0.27] | 4.9%
Beer et al. 2006 | 0 | 16 | 0.00 | [0.00; 0.21] | 4.3%
Brandt et al. 2009 | 24 | 105 | 0.23 | [0.15; 0.32] | 5.1%
Carruthers et al. 2002 | 203 | 203 | 0.0 | 0.0% | 0.0%
Carruthers et al. 2003 | 59 | 59 | 0.0 | 0.0% | 0.0%
Carruthers et al. 2005 | 80 | 80 | 0.0 | 0.0% | 0.0%
Carruthers et al. 2007 | 2 | 20 | 0.10 | [0.01; 0.32] | 4.5%
Carruthers et al. 2013 | 13 | 184 | 0.07 | [0.04; 0.12] | 5.1%
De Boulle et al. 2018 | 344 | 631 | 0.55 | [0.51; 0.58] | 5.2%
Fagien et al. 2007 | 1 | 35 | 0.03 | [0.00; 0.15] | 4.8%
Fagien et al. 2017 | 150 | 290 | 0.52 | [0.46; 0.58] | 5.2%
Grimes et al. 2009 | 4 | 31 | 0.13 | [0.04; 0.30] | 4.7%
Hanke et al. 2013 | 22 | 182 | 0.12 | [0.08; 0.18] | 5.1%
Harii et al. 2008 | 17 | 90 | 0.19 | [0.11; 0.29] | 5.0%
Kane et al. 2009 | 51 | 544 | 0.09 | [0.07; 0.12] | 5.2%
Kane et al. 2015 | 16 | 250 | 0.06 | [0.04; 0.10] | 5.1%
Moers-Carpi et al. 2012 | 3 | 224 | 0.01 | [0.00; 0.04] | 5.1%
Monheit et al. 2007 | 169 | 279 | 0.61 | [0.55; 0.66] | 5.2%
Rzany et al. 2006 | 11 | 146 | 0.08 | [0.04; 0.13] | 5.1%
Sattler et al. 2010 | 14 | 381 | 0.04 | [0.02; 0.06] | 5.2%
Solish et al. 2016 | 40 | 116 | 0.34 | [0.26; 0.44] | 5.1%
Wu et al. 2009 | 55 | 170 | 0.32 | [0.25; 0.40] | 5.1%

Random effects model | 4268 | 0.16 | [0.08; 0.26] | 100.0%

Heterogeneity: $I^2 = 98\%$, $\chi^2 = 0.0763$, $p < 0.01$
# Breakdown of Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache and Migraine</td>
<td>269 (6.3%)</td>
</tr>
<tr>
<td>Local skin reactions (bruising or hematoma at the injection site)</td>
<td>163 (3.8%)</td>
</tr>
<tr>
<td>Facial neuromuscular symptoms</td>
<td>141 (3.3%)</td>
</tr>
<tr>
<td>Pulmonary symptoms</td>
<td>91 (2.1%)</td>
</tr>
<tr>
<td>Ocular symptoms</td>
<td>39 (0.9%)</td>
</tr>
<tr>
<td>Cardiovascular symptoms</td>
<td>22 (0.5%)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>18 (0.4%)</td>
</tr>
<tr>
<td>Remote skin reactions</td>
<td>11 (0.3%)</td>
</tr>
<tr>
<td>Face asymmetry</td>
<td>6 (0.1%)</td>
</tr>
<tr>
<td>General symptoms such as fatigue</td>
<td>6 (0.1%)</td>
</tr>
</tbody>
</table>
onabotulinum

Study | Cases | Total | Proportion | 95%-CI | Weight
--- | --- | --- | --- | --- | ---
Beer et al. 2006 | 0 | 16 | 0.00 | [0.00; 0.21] | 7.4%
Carruthers et al. 2007 | 2 | 20 | 0.10 | [0.01; 0.32] | 7.6%
De Boulle et al. 2018 | 344 | 631 | 0.55 | [0.51; 0.58] | 8.8%
Fagien et al. 2007 | 1 | 35 | 0.03 | [0.00; 0.15] | 8.1%
Fagien et al. 2017 | 150 | 290 | 0.52 | [0.46; 0.58] | 8.7%
Grimes et al. 2009 | 4 | 31 | 0.13 | [0.04; 0.30] | 8.0%
Harli et al. 2008 | 17 | 90 | 0.19 | [0.11; 0.29] | 8.5%
Kane et al. 2015 | 8 | 128 | 0.06 | [0.03; 0.12] | 8.6%
Moers-Carpi et al. 2012 | 1 | 112 | 0.01 | [0.00; 0.05] | 8.6%
Sattler et al. 2010 | 5 | 97 | 0.05 | [0.02; 0.12] | 8.5%
Solish et al. 2016 | 40 | 116 | 0.34 | [0.26; 0.44] | 8.6%
Wu et al. 2009 | 55 | 170 | 0.32 | [0.25; 0.40] | 8.6%
Random effects model | 1736 | | 0.16 | [0.06; 0.30] | 100.0%
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.0784$, $p < 0.01$
<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Total</th>
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</thead>
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<tr>
<td>Carruthers et al. 2013</td>
<td>13</td>
<td>184</td>
<td>0.07</td>
<td>[0.04; 0.12]</td>
<td>20.6%</td>
</tr>
<tr>
<td>Hanke et al. 2013</td>
<td>22</td>
<td>182</td>
<td>0.12</td>
<td>[0.08; 0.18]</td>
<td>20.6%</td>
</tr>
<tr>
<td>Kane et al. 2015</td>
<td>8</td>
<td>122</td>
<td>0.07</td>
<td>[0.03; 0.13]</td>
<td>18.5%</td>
</tr>
<tr>
<td>Moers-Carpi et al. 2012</td>
<td>3</td>
<td>112</td>
<td>0.03</td>
<td>[0.01; 0.08]</td>
<td>18.0%</td>
</tr>
<tr>
<td>Sattler et al. 2010</td>
<td>9</td>
<td>284</td>
<td>0.03</td>
<td>[0.01; 0.06]</td>
<td>22.4%</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>884</strong></td>
<td></td>
<td><strong>0.06</strong></td>
<td><strong>[0.03; 0.10]</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 76\%$, $\tau^2 = 0.0046$, $p < 0.01$
abobotulinum

<table>
<thead>
<tr>
<th>Study</th>
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<td>Ascher et al. 2004</td>
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<td>0.07</td>
<td>[0.03; 0.14]</td>
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<td>Ascher et al. 2005</td>
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<td>50</td>
<td>0.14</td>
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<td>16.1%</td>
</tr>
<tr>
<td>Brandt et al. 2009</td>
<td>24</td>
<td>105</td>
<td>0.23</td>
<td>[0.15; 0.32]</td>
<td>16.6%</td>
</tr>
<tr>
<td>Kane et al. 2009</td>
<td>51</td>
<td>544</td>
<td>0.09</td>
<td>[0.07; 0.12]</td>
<td>17.0%</td>
</tr>
<tr>
<td>Monheit et al. 2007</td>
<td>169</td>
<td>279</td>
<td>0.61</td>
<td>[0.55; 0.66]</td>
<td>16.9%</td>
</tr>
<tr>
<td>Rzany et al. 2006</td>
<td>11</td>
<td>146</td>
<td>0.08</td>
<td>[0.04; 0.13]</td>
<td>16.7%</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>1226</strong></td>
<td></td>
<td><strong>0.18</strong></td>
<td>[0.04; 0.39]</td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.0803$, $p < 0.01$
practitioner

- Doctor
- Nurse
- Other

- 7 studies reported that the injections were administered by a doctor
- No further information was provided re specialty
discussion
discussion points

- adverse events related to glabellar and forehead BoNT-A injection is approximately 16%
- local skin reactions and headache were the most commonly reported complications in both BoNT-a and placebo, suggests these may be administration related
- different definitions for complications
- similar efficacy and safety profile across ona, inco and abo – botulinum toxin
lack of standardized reporting of complications

• MHRA database of complications found 188 complications over a 30-year period (1991 – 2020)
• underreporting of complications suspected given previous findings
• significant variations in reporting structures despite the use of the yellow card reporting scheme
• future work could look to create a framework around capturing cosmetic complications related to injectables
limitations

- search strategy focused on complications
- some studies included patients who were not BoNT-A naïve
- no consistent reporting of complications
- treatment related or treatment emerged complications not distinguished
thank you

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