Microneedle Delivery of Propranolol and Timolol to Treat Infantile Hemangiomas

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Presentation outline

• Introduction
• Hypothesis/goal
• Methods
• Results
• Discussion/conclusion
• Limitations
• Future Applications
• Acknowledgements
Infantile Hemangiomas

- Benign vascular tumor in pediatric patients
- Goes away over several years
- Cosmetically concerning
- Some require treatment due to:
  - Obstruction of airways & eyes
  - Scarring or disfiguring on child's body parts

Source: Medscape.com
Current Treatment Options

• Oral corticosteroids --> NOT used first line
• Propranolol
• Timolol eyedrops
• Problem with treatments
  • Risk of systemic drug delivery systemic side effects: hypotension, bradycardia, hypoglycemia & bronchospasm from oral beta-blocker(s)
  • Frequent complications from oral corticosteroid: increased risk of infections & GI upset
  • Topical Beta-blockers good for small, superficial hemangiomas only
Microneedle (MN) Technology

- Micron-scale projections used to deliver drug deeper into skin
- Usage allows for the avoidance of systemic side-effects
- Penetration allows for drug targeting in dermis of skin
  - Inflammatory markers for hemangiomas present here
  - Microneedles can aid in drug delivery to this area

Source: thecoolgadgets.com
Hypothesis/Goal

• **Hypothesis**: Microneedle delivery of propranolol and timolol will increase the skin’s concentration of the drug in vitro compared to topical propranolol and timolol eye drops.

• **Goal**: Developing dissolving microneedle formulations of propranolol & timolol to increase drug delivery from the microneedle formulations in the skin, avoiding systemic adverse events to improve safety for treatment of small, localized infantile hemangiomas
Methods

• Made two microneedle formulations for each drug (propranolol & timolol) in 100-microneedle mold, 350 microns in length:
  • Formula 1: Polyvinyl alcohol/Polyvinylpyrrolidone (PVA/PVP) + drug agents
  • Formula 2: PVP + PEG-400 + drug agents
  • Microneedles made by centrifugation & drying

• Efficacy of microneedle formulation tested by diffusion studies w/ standard thickness of excised pig skin

• Microneedle permeation into the skin tested by Transepidermal water loss test (TEWL)
Methods (cont.)

• Solid needle dermarollers served as the control
  • 500 µm and 250 µm
• Compounded 0.5% w/v propranolol in PBS
• Standard 0.5% timolol ophthalmic drops
Methods – Diffusion Study

• Pig skin (membrane) was treated with MN (donor compound)
• Receiver solution: 10% ethanol in HEPEs buffer modified with Hank’s balanced salts
  • pH of 7.4 at 32°C
• Receiver solution collected over 24 hours
• The solution and skin were tested for the presence and quantity of drug by mass spectroscopy
Diffusion Study Set-up
Methods - TEWL

• Transepidermal water loss test
  • Measures water lost through the skin

• Treated different pieces of pig skin with the PVA/PVP MN, PVP only MN, and dermarollers

http://www.courage-khazaka.de
Results - 500 µm Dermaroller

• Increase in skin concentrations
• Increase in receiver solution concentrations
Results - 250 µm Dermaroller

- Increase in skin concentrations
- Increase in receiver solution concentrations
Results - PVA/PVP MN

- Increase in skin concentrations
- Increase in receiver solution concentrations

<table>
<thead>
<tr>
<th></th>
<th>Propranolol (non-occluded)</th>
<th>Propranolol (occluded)</th>
<th>Timolol (non-occluded)</th>
<th>Timolol (occluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading into MN array (umol)</td>
<td>1.74 ± 0.18</td>
<td>1.74 ± 0.18</td>
<td>1.19 ± 0.18</td>
<td>1.19 ± 0.18</td>
</tr>
<tr>
<td>Amount of drug remaining in array after diffusion study (umol)</td>
<td>1.37 ± 0.25</td>
<td>1.32 ± 0.18</td>
<td>0.28 ± 0.03</td>
<td>0.29 ± 0.01</td>
</tr>
<tr>
<td>% of drug remaining in the MN array</td>
<td>79.11 ± 14.37</td>
<td>76.22 ± 10.27</td>
<td>23.31 ± 2.14</td>
<td>24.02 ± 75.98</td>
</tr>
</tbody>
</table>
Results – PVP MN

- Skin concentrations were quantifiable
- Detectable levels in the receiver solution found, not in very high amounts

<table>
<thead>
<tr>
<th>Skin concentrations (μmol drug/g skin)</th>
<th>Propranolol</th>
<th>Timolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.017 ± 0.002</td>
<td>0.021 ± 0.016</td>
</tr>
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</table>
Results - TEWL

- **PVA/PVP**
  - No significant difference between intact and MN treated skin

- **PVP**
  - All had a significant increase in water loss

- **Dermarollers**
  - All had a significant increase in water loss
Discussion/Conclusion

• Both dermarollers increased the skin and receiver solution concentrations as expected
• PVA/PVP MN failed to penetrate the skin
  • Did not deliver drug
• PVP MN successfully delivered drug into the skin
  • Brittle
• Further studies are needed to optimize the dissolvable microneedle formulation to fabricate a strong and sharp microneedle capable of penetrating the epidermis, and providing therapeutic slow and sustained drug release
Limitations

• No standardized application process

• Skin is absent of disease state

• Time
Future implications

- Vaccinations?
- Insulin delivery?
- Topical Cancer treatment(s)?
- More studies are needed!
Acknowledgements

• Megan Kelchen, PhD. Candidate
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