Microbubbles accelerate thrombolysis in peripheral arterial occlusions: how does the technology work?

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Disclosure

Speaker name:
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I have the following potential conflicts of interest to report:

☐ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

☒ I do not have any potential conflict of interest
Introduction

- Acute peripheral arterial occlusions
- Therapy: catheter directed *thrombolytic infusion with urokinase, (r)tPA:
  - NL: urokinase
  - Time consuming
  - Cave: major haemorrhagic complications 6-13%, 2% intracranial haemorrhages*
Better, Safer and Faster Thrombolysis is needed
• Heavy gas filled particles with lipid shell
• Tiny microbubbles **oscillate** when subjected to low intensity ultrasound (US) and can **cavitate** when subjected to high intensity US

Courtesy to N de Jong
Advantages of microbubbles

Non-specific mechanical effects → thrombus breakdown
due to mechanical force of microbubbles + ultrasound
Advantages of microbubbles

Carry thrombolytics to the specific thrombus

NO CATHETER NEEDED
In vitro study

= FLUORESCENT LABELED UROKINASE

INCORPORATED IN THE BUBBLE

ON THE OUTER LIPID SHELL

MORE PRECISE DELIVERY AND NO NEED FOR A CATHETER
How does the technology work?
Aim

Non-specific mechanical effects: thrombus breakdown due to mechanical force of microbubbles + ultrasound

Improve thrombolysis for acute peripheral occlusions by using microbubbles and concomitant application of ultrasound

Reduce therapy time and thrombolytic dose
Methods

• Animal model: pilot study
• Yorkshire pigs 60-80kg
• Thrombus: 100U Bovine Thrombine
**Control group**

- **Catheter**
  - Microbubbles 5x5mL in 1 hour
  - High intensity ultrasound
  - N=4

- **Catheter**
  - Microbubbles 5x5mL in 1 hour
  - Local low intensity ultrasound
  - N=6

- **EKOS catheter**
  - Microbubbles 5x5mL in 1 hour
  - High intensity ultrasound
  - N=4

- **Targeted Microbubbles carrying UK:**
  - 5x5 mL in 1 hour
  - N=5

**Urokinase:**
- 500,000 IU UK bolus
- 50,000 IU UK/ hour for 3 hours
End points

- Flow distal to the occlusion in the external iliac artery
- Thrombus weight at the end of the experiment
- Haemorrhagic complications
## Results

### Flow in the external iliac artery 3 hours after therapy

<table>
<thead>
<tr>
<th>Groups</th>
<th>Reperfusion at the end of the experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group: standard therapy: catheter + UK</td>
<td>1/4</td>
</tr>
<tr>
<td>microbubbles + ultrasound + catheter + UK</td>
<td>4/6</td>
</tr>
<tr>
<td>microbubbles + ultrasound + EKOScatheter + UK</td>
<td>4/4</td>
</tr>
<tr>
<td>targeted microbubbles carrying UK + ultrasound</td>
<td>3/5</td>
</tr>
</tbody>
</table>
Results

Thrombus weight (gr) at the end of the experiment

No haemorrhagic complications were observed during autopsy.
MUST-TRIAL
MICROBUBBLE & ULTRASOUND ACCELERATED THROMBOLYSIS

n = 20

UROKINASE
START 500,000 IU
HOURLY 50,000 IU

6 HOURS
VAS PAIN SCORES
DUPLEX ECHOGRAHY
MICROCIRCULATION BY LASER DOPPLER
DAILY ANGIOGRAPHY
Conclusion

- Application of ultrasound with infusion of microbubbles could improve thrombolytic therapy

- Targeted microbubbles carrying urokinase is a potential option for thrombolysis without the need for a catheter
Project group

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