Implantable ultrasound device for repeated opening of the blood brain barrier: A promising technology for drug delivery into the brain

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Brain tumors = a dramatic prognosis

- Why? The blood-brain barrier (BBB) limits the efficacy of chemotherapy
- US demonstrated to induced BBB opening in pre-clinical studies using pulsed ultrasound + US contrast agents
  - Skull is main problem for clinical application
  - MRguided Extracorporeal US Phased Arrays (McDannold et al. 2012, Cancer Research, …)
  - Heavy method for routine repeated BBB opening at each chemotherapy session

Figure from Vykhodtseva et al. (2008)
Original concept

Use skull burr hole (1-cm) after tumor resection for an implantable ultrasound device to achieve simple, repeated BBB openings
Implantable US Device: Concept

1. 1 MHz, 10 mm diameter transducer

2. Transdermal needle connection

3. External Generator

1. Ultrasound device is implantable, MR-compatible, no energy source

2. Power supplied by needle connection

3. External generator used for US-activation and treatment control
Preclinical trials – Short term safety

Rabbits

Toxicity after 7 days evaluated after BBB opening.

Dogs

No adverse effects observed on MR and histology.
No behavior modification.
MR at day 7 showed normal BBB.

Previous pre-clinical studies show safety of BBB opening protocol in short-term (0-7 days) with single sonication/opening
Preclinical trials – Drug delivery

- Experiments in rabbits
- Opening of the BBB with US 5 minutes after injection of chemotherapy
Goal of the present study

• Perform repeated (7 times) BBB opening
• Evaluate long term safety and toxicity
• in primates
Experimental protocol

• 3 primates (2 baboons and 1 macaque)

• Protocol:
  – Implantable ultrasound device on top of motor cortex in a typical neurosurgeon’s burr hole
  – Repeated BBB openings every 2 weeks during 3 months (7 BBB opening sessions)

• Follow up
  – Contrast enhanced MRI
  – Electrophysiology
  – PET
  – Histology
Exposure conditions

- Transdermal electrical supply at each session
- Flat piston, 1 cm in diameter, 1 MHz
- 0.6-0.8 MPa, 25 ms pulse, 1 Hz (DC=2.5%), 120 s
- SonoVue (0.1 cc/kg)

Simulated pressure field in water
Monitoring with T1-w contrast-enhanced MRI

BBB opening observed immediately after each sonication
Electrophysiologic monitoring

Before and after each BBB opening session

- **Electro-Encephalogram**
  - No epileptic signs (foci, ii-spike)
  - No cognitive decline
  - No medicinal encephalopathy

- **Somatosensory Evoked Potentials**
  - No pathologic conduction
  - No amplitude modification

►► No neural hyper excitability
►► No neural conduction abnormality
FDG$_{18}$ / glucose uptake PET monitoring

Day 0  Day 1  Day 45  Day 60  Day 75

PET scans showed no significant changes in cerebral metabolism of glucose

(n=15, after BBB opening)
DPA$_{714}$ PET monitoring

- At D7 post BBB opening

➤➤ No significant inflammation at 7 days post US/BBB opening
Behavior & Neurological status

- n=3x16: baseline, before and after 7 sonications, endline
- BBB opening was performed in the primary motor cortex

- Normal Behavior in all 3 animals during the 4 months
- Normal motricity neurological status
Histology H&E at month 4

No signs of hemorrhagic processes or ischemia
• Integrity of the vessel walls was unchanged.
• Extravasation of a few red blood cells in 1 primate though not observed on MRI.
Conclusions

**SonoCloud®**: an promising (efficient and safe) implantable ultrasound device developed for repeated BBB opening on clinical routine patients

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