Sonothrombolysis for acute ischemic stroke

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Carlos A. Molina
TCD in acute stroke
Advantages of TCD-TCCS in acute stroke

Location of arterial occlusion

Evaluation of collateral flow

Recanalization monitoring

Re-occlusion

Enhance the fibrinolytic action of tPA
Recanalization monitoring
TCD continuous monitoring

Correlation with clinical course and outcome
Determination of recanalization

TIBI 0

TIBI 1

No recanalization

TIBI 2

TIBI 3

Partial recanalization

TIBI 4

TIBI 5

Complete recanalization
Dynamic of tPA-induced clot dissolution in acute stroke

Delgado-Mederos et al Eur J Neurol 2005
Re-occlusion is usually defined as a worsening in 1 grade in the TIBI flow grading system after a previously documented recanalization.
Sonothrombolysis
Reversible changes in fibrin mesh

Before

During

After

Sonothrombolysis
Better tPA penetration and distribution

Flow turbolences surrounding the thrombus: microstreaming
Sonothrombolysis
Better tPA penetration and distribution

Binding affinity tPA-fibrin
Sonothrombolysis
Better tPA penetration and distribution

Thrombus dissolution
Basal
60 min
120 min
Ultrasound Enhanced Thrombolysis
Animal models

Ishibashi y cols Stroke 2002
# US-enhanced thrombolysis in acute stroke

<table>
<thead>
<tr>
<th>Trial</th>
<th>Transducer</th>
<th>Tissues Exposed</th>
<th>$sICH$</th>
<th>CR</th>
<th>mRS 0-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOTBUST</td>
<td><img src="image1" alt="CLOTBUST transducer" /></td>
<td><img src="image2" alt="CLOTBUST tissue" /></td>
<td>4.8%</td>
<td>38%</td>
<td>42% completed</td>
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<tr>
<td>n = 126</td>
<td>2 MHz single beam</td>
<td></td>
<td></td>
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<tr>
<td>Eggers et al.</td>
<td><img src="image3" alt="Eggers transducer" /></td>
<td><img src="image4" alt="Eggers tissue" /></td>
<td>18%</td>
<td>27%</td>
<td>27% no pre-determined sample size</td>
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<tr>
<td>n = 25</td>
<td>2-4 MHz multi-beam</td>
<td></td>
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<tr>
<td>TRUMBI</td>
<td><img src="image5" alt="TRUMBI transducer" /></td>
<td><img src="image6" alt="TRUMBI tissue" /></td>
<td>36%</td>
<td>&lt;22%</td>
<td>? terminated</td>
</tr>
<tr>
<td>n = 26</td>
<td>300 KHz multi-beam</td>
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<td></td>
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</tbody>
</table>
TRUMBI trial

- Randomized trial of 26 patients < 6h

- Low-frequency high intensity US during 90 minutes
  - 300 Khz
  - 7 W/cm²
  - Mechanical Index < 0.2
  - Thermal index < 0.5

- Stopped. SICH
  - 5/14 (42%) tPA + US

Daffertshofer Stroke 2005
TRUMBI trial
Intracranial hemorrhage

Daffershofer Stroke 2005
Ultrasound-Enhanced Systemic Thrombolysis for Acute Ischemic Stroke

Andrei V. Alexandrov, M.D., Carlos A. Molina, M.D., James C. Grotta, M.D., Zsolt Garami, M.D., Shiela R. Ford, R.N., Jose Alvarez-Sabin, M.D., Joan Montaner, M.D., Maher Saqqur, M.D., Andrew M. Demchuk, M.D., Lemuel A. Moyé, M.D., Ph.D., Michael D. Hill, M.D., and Anne W. Wojner, Ph.D., for the CLOTBUST Investigators*
CLOTBUST trial has demonstrated that diagnostic TCD (2 Mhz frequency) increase recanalization rates in acute stroke patients treated with t-PA

Alexandrov et al. *NEJM* 2004
Sustained Complete Recanalization: TCD TIBI 5 Flow at 30 min Intervals

Target
Control

p = 0.003
CLOTBUST Limitations

- Unblinded sonographers
- Lack of confirmation of occlusion and recanalization with CTA or MRA
- Sample size was not powered to assess clinical outcome
TCCS-enhanced thrombolysis

37 patients tPA treated:

19 US group
tPA + 1 hr TCCS

18 noUS group
tPA

Eggers et al Stroke 2008
Microbubbles

Gas / air

shell

Ferrara K et al. UC-Davis
MB-enhanced sonothrombolysis

- Ultrasound-accelerated thrombolysis may be further enhanced by MB
  - lowering the threshold for cavitation
  - Providing a nucleus for cavitation
MB-enhanced sonothrombolysis
MB-enhanced sonothrombolysis
Microbubble Administration Accelerates Clot Lysis During Continuous 2-MHz Ultrasound Monitoring in Stroke Patients Treated With Intravenous Tissue Plasminogen Activator

Carlos A. Molina, MD, PhD; Marc Ribo, MD, PhD; Marta Rubiera, MD; Joan Montaner, MD, PhD; Esteban Santamarina, MD; Raquel Delgado-Mederos, MD; Juan F. Arenillas, MD, PhD; Rafael Huertas, MD; Francisco Purroy, MD; Pilar Delgado, MD; José Alvarez-Sabín, MD, PhD
Patients and Methods

345 ischemic strokes evaluated < 3h

103 patients with MCA occlusion on TCD

- tPA 33%
- tPA + US 33%
- tPA + US + MB (34%)

2’ 20’ 40’

Leovist 400mg/ml
Recanalization after microbubbles

Persistent flow improvement after microbubbles infusion.
Timing of MB-enhanced recanalization in Basilar Occlusion

Stroke Unit Vall d´Hebron

Pagola et al. Stroke 2007
Timing of recanalization after sonothrombolysis with tPA and TNK

Molina et al ESC 2008
US microbubbles destruction and BBB permeability
Aim

To evaluate the risk of hemorrhagic transformation in acute stroke patients (< 6 h) treated with sonothrombolysis potentiated by microbubbles
Patients with MCA occlusion

480

Historical control group
98 patients

MB group (Levovist®)
188 patients
Hemorrhagic transformation

- HI1+HI2
- PH1+PH2
- sICH

TPA+US+MB
TPA+US

p=0.026
OR 5.8 95% CI 2.1-65

p=0.8

p=0.58
MB administration was associated with a higher degree of clinical improvement at 24h and higher rate of HI1-HI2, but it did not increase the risk of symptomatic ICH.

Dinia et al.
International Stroke Conference,
New Orleans, 2008
LMCA occlusion
NIHSS score 12

Blooming effect of MBs

Time: 3 min 15 sec
LMCA occlusion
NIHSS score 12

End of Blooming
Time: 4 min 35 sec
LMCA occlusion
NIHSS score 9

TIBI 3 at 38 mm
Time: 6 min 32 sec
LMCA occlusion
NIHSS score 5

TIBI 4 at 46 mm
Time: 8 min 51 sec
Complete Left MCA recanalization
NIHSS score 1
Time: 10 min 18 sec

MES

TiBi 5 at 38 mm
Complete Left MCA recanalization
NIHSS score 1
Time: 11 min 12 sec

TIBI 5 at 38 mm
TUCSON TRIAL
Transcranial Ultrasound in Clinical SONolysis

A Phase 1-2, Randomized, Placebo Controlled, Open-Label, Dose Escalation Study to Evaluate the Safety, Tolerability, and Activity of Ascending Single Doses of MRX-801 with Continuous Ultrasound Administration in subjects with Acute Ischemic Stroke Receiving Treatment with Intravenous Tissue Plasminogen Activator.
Stroke 3-6h.+ IA tPA.

Endovascular lysis with US (EKOS)

Increase of the surface of thrombus exposed to tPA.

*AJNR 24:534–538, 2003*
Loaded-microbubbles
targeted-microbubbles
Conclusions

Diagnostic (2MHz) US accelerates thrombolysis with tPA and TNK in acute stroke

MB induces further acceleration of US-enhanced thrombolysis

- Faster and more complete recanalization
- Trend to better short-term clinical outcome

A multicenter trial of MB-enhanced sonothrombolysis to verify these results is necessary