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Thrombolysis with Ultrasound

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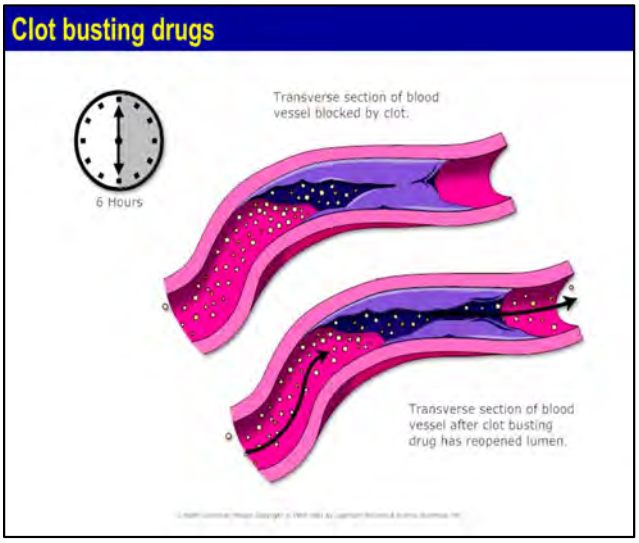
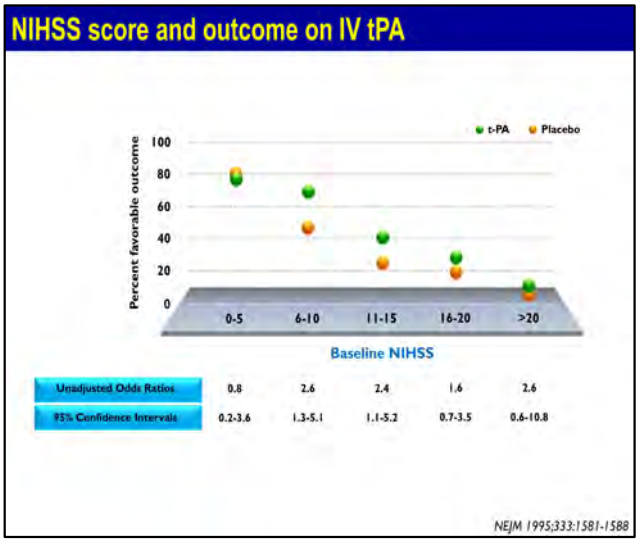
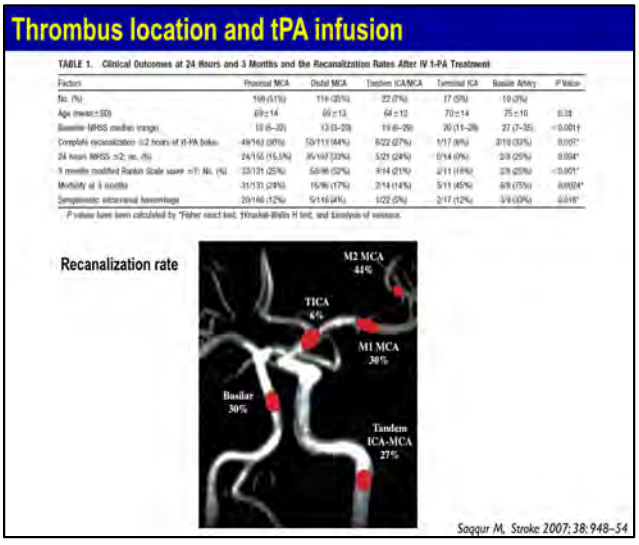
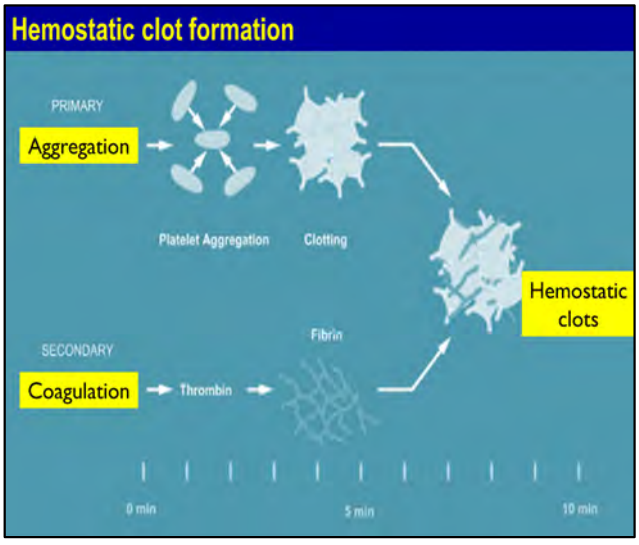
홍 지 만









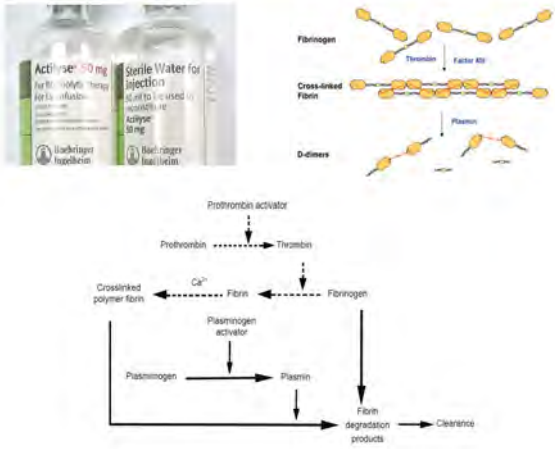
Basic concepts of sonothrombolysis

Without ultrasonic energy
- Normal hemostatic clots
- ↓ Plasminogen receptor sites

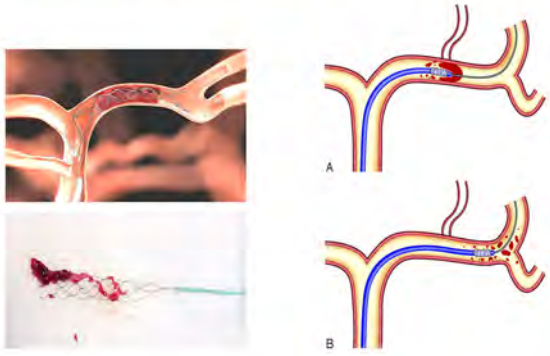
With ultrasonic energy
- Fibrin strands to thin
- Plasminogen receptor sites ↑

With ultrasonic energy & thrombolytic
- Fibrin strands to thinner
- Plasminogen receptor sites↑
- More permeable thrombus

Tissue plasminogen activator (t-PA)



Stent retriever vs. clot-busting



Ultrasound biomedical effects

- Focused high-energy ultrasound pulses can be used to break calculi (kidney stones and gallstones into fragments)
- Accelerate the effect of drugs in a targeted area

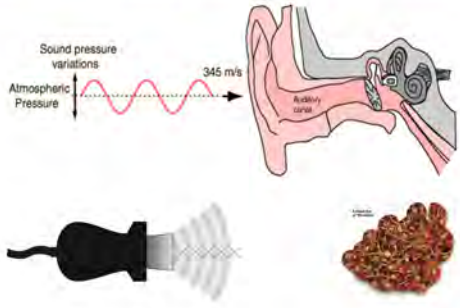
General ultrasound advantages

- Convenience
- Cost
- Safety
- Realtime display

General challenges

- Image contrast
- Resolution

Ultrasonic mechanical pressure wave

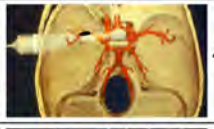
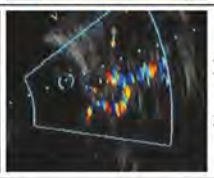


- Fluid streaming around clot surface
- Disaggregation of fibrin fibers
- Creating more binding sites for tPA without heating or cavitation

Low frequency tPA-induced thrombus dissolution

- Emergency room to continuous monitor tPA effects
- Localization of arterial occlusion
- Assessment of recanalization or reocclusion at bedside
- Showing real-time flow findings (embolization, collateralization ..)

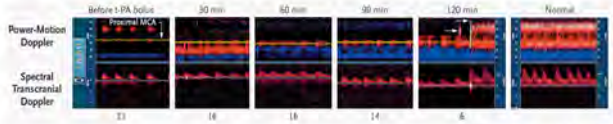
Reported controlled clinical trials in AIS

Trial	Transducer	Tissues Exposed	sICH	CR	mRS 0-1
CLOTBUST n = 126 2 MHz single beam			4.8%	38%	42%
			completed		
Eggers et al. n = 25 2-4MHz			18%	27%	27%
			no pre-determined sample size		
TRUMBI n = 26 300 KHz multi-			36%	<22%	?
			terminated		

CLOTBUST (Combined Lysis Of Thrombus in Brain Ischemia using transcranial Ultrasound and Systemic TPA)

- Phase II, Clnical RCT, multicenters, international trials (Houston, Barcelona, Edmonton, Calgary)
- Prespecified safety and signal of efficacy end-points
- Pre-determined sample size of 63 patients per group
- MCA occlusion on pretreatment TCD, standard dose of TPA (0.9 mg/kg), 1:1 radomization
- Safety end-point: symptomatic brain hemorrhage (sICH) with 4 or more NIHSS
- Complete recanalization on TCD
- Improvement of >10 NIHSS points within 2 hours after TPA bolus

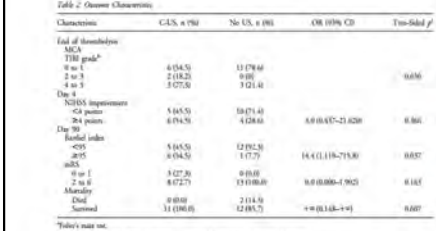
- A total of 126 patients (17 points of median NIHSS)
- sICH: 4.8% (TCD) vs 4.8% (Control)
- Complete recanalization: 46% (TCD) vs 18% (Control), p<0.001
- 3-month prognosis (mRS 0-1): 42% (TCD) vs 29% (Control), p=0.20

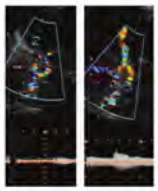


Alexandrov AV, NEJM 2004; 351:2170-8

TCCS (Transcranial Color-Coded Sonography) trial

- Single center trial (Germany)
- MCA occlusion on pretreatment TCCS, standard dose of TPA (0.9 mg/kg)
- 2-4 MHz sector transducer (S4 probe; Philips medical), acoustic power in pulsed waved 179mW/cm^2
- Continuously monitored with TCCS over 1 hour
- A total of 25 patients: 11 TCD, 14 control
- ICH: 45% (TCCS) vs 7% (Control)





Eggers J. Ann Neurol 2003; 53: 797-800

TRUMBI (TRanscranial Low-frequency Ultrasound Mediated thrombolysis in Brain Ischemia study)

- Multi-center trial (Germany)
- MCA occlusion on low-frequency ultrasound (300kHz), standard dose of TPA (0.9 mg/kg) within 6 hours

Figure 1. The transducer has 4 elements (A to D) arranged in a diamond pattern. These operated in pairs to insonify a particular region of the target anatomy. Thus, the CB pair or the CD pair (depending on the side of the head where the transducer is positioned) sonicate the circle of Willis area and the M1 segment. The DB pair covers the M2 and proximal M3 segment. The AD and AB pairs are targeted at the mid and distal M3 segments. The focus was set to the contralateral M1 segment (≈10 cm away from the probe surface). The effective ultrasound field around the beam axis at the sonicated target area covered ≈8 cm in frontal-occipital and ≈6 cm in cranio-caudal direction.

TABLE 2. Hemorrhages

	tPA Only MRI	Ultrasound Plus tPA MRI
None	7	1
HT1	3	8
HT2	2	2
PH2		2
HT1 + SAH		1
PH2 + SAH		1
PH1 + HT1 + VH		1
Total	12	14

VH indicates ventricular hemorrhage.

Daffertshofer M, Stroke 2005; 36: 1441-1446

With tPA + sonography + Microbubbles

Reasons for usage

- Strong acoustic signal
- Enhancement of tPA effectiveness

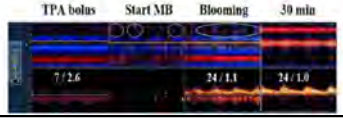
Safety? (bends: diver, astronaut)

- Size: < the diameter of the smallest vessel
- Coating: surfactant or polymer shells to prevent them dissolving
- Core gas: low solubility, non-toxic gas, not normally present in the body

Reported trials of MPUS (microsphere-potentiated ultrasound-enhanced thrombolysis)

Trial	F	ECA	Design	R	REC.**	AsxICH**	sICH**	Outcome at 3 months
TCD								
Molina et al.[40]	2 MHz	galactose-based	US/MS/tPA (n=48) vs. US/tPA (n=37) vs. tPA (n=36)	N	71%	23%	3%	56% (mRS 0-2)
Alexandrov et al.[42]	2 MHz	perflutren-lipid	US/MS/tPA (n=12) vs. US/tPA (n=3)	Y	42%	25%	0%	40% (mS 0-1)
TCCD								
Larrue et al.[43]	2 MHz*	galactose-based	US/MS/tPA (n=9) vs. TPA (n=11)	Y	48%	78%	0%	NA
Perren et al.[45]	2 MHz*	phospholipid -encapsulated sulphur hexafluoride	US/MS/tPA (n=11) vs. tPA (n=15)	N	64%	NA	9%	NA

US: Continuous Ultrasound Monitoring; MS: microspheres; tPA: tissue plasminogen activator; R: Randomization; REC: recanalization at the end of TCD monitoring; sICH: symptomatic intracranial hemorrhage; AsxICH: asymptomatic intracranial hemorrhage; mRS: modified Rankin Scale; NA: not available. *patients received monitoring with a pulsed wave 2 MHz phased array Doppler and intermittent exposure to dual frequency duplex; **in the active treatment group (microsphere-potentiated ultrasound-enhanced systemic) thrombolysis; ***at three months



Tsivgoulis G JCN 2007; 3: 1-8
Meairs S. Stroke 2012; 43:1706-1710

TUCSON (Transcranial ultrasound in clinical sonothrombolysis) trial

Transcranial ultrasound in clinical sonothrombolysis (TUCSON) trial.

Molina CA[1], Barreto AD, Tsivgoulis G, Sierzenski P, Malkoff MD, Rubiera M, Gonzales N, Mikulik R, Pate G, Ostrem J, Singleton W, Manvelian G, Unger EC, Grotta JC, Schellinger PD, Alexandrov AV.

Author information

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Abstract

OBJECTIVE: Microspheres (microS) reach intracranial occlusions and transmit energy momentum from an ultrasound wave to residual flow to promote recanalization. We report a randomized multicenter phase II trial of microS dose escalation with systemic thrombolysis.

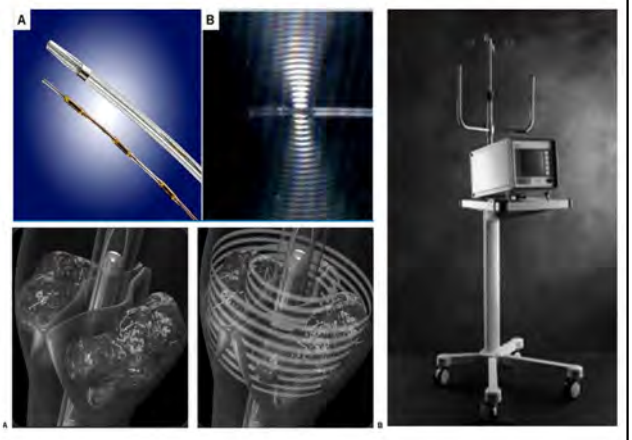
METHODS: Stroke patients receiving 0.9mg/kg tissue plasminogen activator (tPA) with pretreatment proximal intracranial occlusions on transcranial Doppler (TCD) were randomized (2:1 ratio) to microS (MRX-801) infusion over 90 minutes (Cohort 1, 1.4ml; Cohort 2, 2.8ml) with continuous TCD insonation, whereas controls received tPA and brief TCD assessments. The primary endpoint was symptomatic intracerebral hemorrhage (sICH) within 36 hours after tPA.

RESULTS: Among 35 patients (Cohort 1 = 12, Cohort 2 = 11, controls = 12) no sICH occurred in Cohort 1 and controls, whereas 3 (27%, 2 fatal) sICHs occurred in Cohort 2 (p = 0.028). Sustained complete recanalization/clinical recovery rates (end of TCD monitoring/3 month) were 67%/75% for Cohort 1, 46%/50% for Cohort 2, and 33%/36% for controls (p = 0.255/0.167). The median time to any recanalization tended to be shorter in Cohort 1 (30 min; interquartile range [IQR], 6) and Cohort 2 (30 min; IQR, 69) compared to controls (60 min; IQR, 5; p = 0.054). Although patients with sICH had similar screening and pretreatment systolic blood pressure (SBP) levels in comparison to the rest, higher SBP levels were documented in sICH+ patients at 30 minutes, 60 minutes, 90 minutes, and 24-36 hours following tPA bolus.

INTERPRETATION: Perflutren lipid microS can be safely combined with systemic tPA and ultrasound at a dose of 1.4ml. Safety concerns in the second dose tier may necessitate extended enrollment and further experiments to determine the mechanisms by which microspheres interact with tissues. In both dose tiers, sonothrombolysis with microS and tPA shows a trend toward higher early recanalization and clinical recovery rates compared to standard intravenous tPA therapy. Ann Neurol 2009;66:28-38.

Molina CA. Ann Neurol 2009; 66:28-38

Endovascular sonothrombolysis



Ultrasound-enhanced thrombolysis meta-analysis

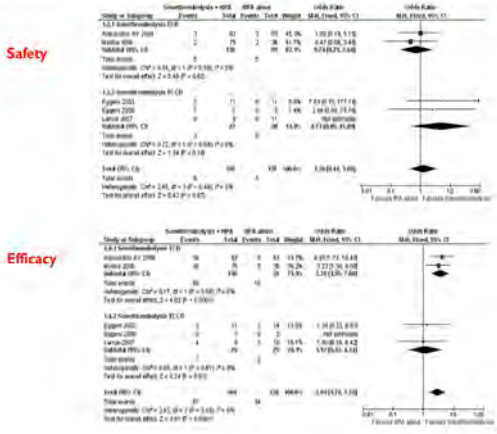
Table 1. Baseline Characteristics of Patients Included in Sonothrombolysis Trials (Controlled and Uncontrolled)

US	Intervention, Active vs Control	R	N*	Occlusion	DTT	Age, Mean (SD)	NIHSS, Median (Range)
TCD							
Alexandrov et al (2004)[4]	TCD+tPA	N	55	Pr. Int. Art* (TCD)	≤3 hr	68±15 y	16 (4-29)
Alexandrov et al (2004)[5]	TCD+tPA vs tPA	Y	63 vs 63	MCA (TCD)	≤3 hr	69±13 y	19 (4-34)
Molina et al (2006)[6]	TCD+tPA+μS vs TCD+tPA vs tPA	N	36 vs 37 vs 36†	MCA (TCD)	≤3 hr	70±12 y	19 (5-23)
Alexandrov et al (2008)[7]	TCD+tPA+μS vs TCD+tPA	Y	12 vs 3	MCA (TCD)	≤3 hr	72±18 y	17 (6-28)
TCCD							
Eggers et al (2003) Preliminary data (n=25)[8]	TCCD+tPA vs tPA	Y	11 vs 14	MCA-M1 TBI 0 (TCCD)	≤3 hr	61±9 y	18 (5-25)
Perren et al (2008)[9]	TCCD+tPA+μS vs TCCD+tPA	N	11 vs 13‡	MCA (TCCD)	≤3 hr	61±27 y	14 (6-28)
Lanoe et al (2007)[10]	TCCD+tPA+μS vs tPA	Y	9 vs 11	MCA (MRA/CTA)	≤3 hr	NA	NA
Eggers et al (2008)[11] Additional data (n=12)	TCCD+tPA vs tPA	Y	7 vs 5	MCA-M1 TBI 0 (TCCD)	≤3 hr	63±16 y	17.5 (12-22)
LFUS							
Daffertshofer et al (2005)[12]	LFTUS+tPA vs tPA	Y	14 vs 12	Pr. Int. Art (MRA)	≤4.35 hr	NA	NA

Variable	tPA	tPA+TCD±μS§	tPA+TCCD±μS¶	tPA+LFUS
Randomized studies				
N of patients	105	78	27	14
sICH (95% CI)*	2.9% (0%–8.4%)	3.8% (0%–11.2%)	11.1% (0%–28.9%)	35.7%† (16.2%–61.4%)
Complete recanalization (95% CI)	17.2% (9.5%–24.9%)	37.2% (26.5%–47.9%)	26.9% (9.9%–44.0%)	NA
Functional independence (mRS 0–1)*	20.6% (12.6%–31.8%)	40.7% (29.1%–53.4%)	22.2% (6.4%–47.6%)	NA
Randomized and nonrandomized studies				
N of patients	141	208	53	14
sICH (95% CI)*	3.5% (0%–8.3%)	3.8% (0%–7.5%)	9.7% (0%–20.7%)	35.7%‡ (16.2%–61.4%)
Complete recanalization (95% CI)	18.8% (12.0%–25.5%)	40.9% (34.2%–47.6%)	42.3% (28.9%–55.7%)	NA
Functional independence (mRS 0–1)*	24.0% (16.8%–33.1%)	40.3% (32.4%–48.8%)	22.2% (6.4%–47.6%)	NA

Tsivgoulis G Stroke 2010; 41 280-287

Ultrasound-enhanced thrombolysis meta-analysis



Tsivgoulis G Stroke 2010; 41 280-287

Ultrasound-enhanced thrombolysis meta-analysis

OBJECTIVES

To assess the evidence on the safety and efficacy of sonothrombolysis in acute stroke.

SEARCH METHODS

Electronic databases and grey literature were searched under different MeSH terms from 1970 to present.

SELECTION CRITERIA

Randomized control trials (RCTs) and case control studies (CCSs) on sonolysis and sonothrombolysis alone or with microsphere in acute stroke patients (>18 old). Outcome measures included complete recanalization (CR) at 1-2 and 24 hours, 3 months modified Rankin Scale (mRS), and symptomatic intracerebral hemorrhage (sICH). Data was extracted to Review Manager software.

RESULTS

Fifty-seven studies were retrieved and analyzed. Ten studies (7 RCTs and 3 CCSs) were included in our meta-analysis, which revealed that sonolysis and sonothrombolysis are safe (OR of sICH: 1.14; 95% confidence interval (CI): 0.56- 2.34;P=0.71) and effective (OR of CR at 1-2 hours: 2.95;95% CI: 1.81-4.81;P<0.00001) and have more than two-fold higher likelihood of favourable long-term outcome (3-month mRS 0-2; OR: 2.20; CI:1.52-3.19;P<0.0001). Further subgroup analysis based on the presence of microsphere revealed that it is safe (OR of sICH: 1.18; CI:0.433.24;P=0.75) and effective (OR of CR: 2.61; CI: 1.36-4.99;P=0.004). Subgroup analysis based on sonolysis revealed to be safe and effective.

CONCLUSIONS

This novel treatment appears safe and effective. The evidence of microsphere as an enhancement of sonothrombolysis is evolving.

Saqqur M, J Neuroimaging 2014; 24: 209-220

CLOTBUST-Hands free

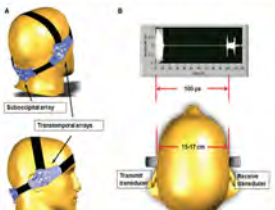
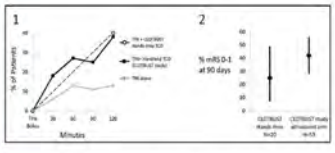


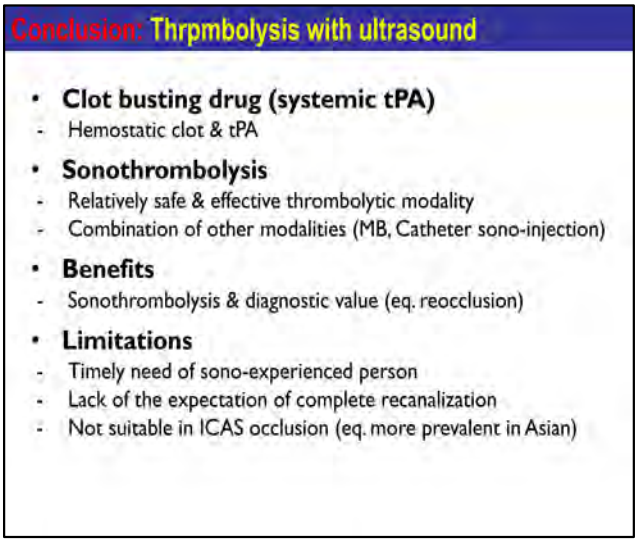
Table 1. Acoustic Parameters for the Operator-Independent Ultrasound Device[17]

Ultrasound Parameters	Value (Unit)
Frequency, and any modulation	2 MHz (pulsed)
Derated I_{SPTA} intensity (for comparison to FDA limits)	207 mW/cm² max
Total power	32 mW average
Pulse duration	5 μs (10 cycles)
Pulse repetition frequency	8.3 kHz
Beam width, –6 dB, min and at region of interest	4.5 mm at 27 mm 6 mm at 45 mm
Aperture size and shape	10 mm, circular
Focal distance (or unfocused)	30 mm
Distance from transducer to region of interest	45 mm
Max peak rarefactional pressure (in water /in situ)	455 kPa/100 kPa
Mechanical/thermal index, max	0.23 MI, 0.81 TIC

FDA indicates Food and Drug Administration; I_{SPTA}, Spatial Peak Temporal Average Intensity; MI, mechanical index; TIC, thermal index for cranial bone.



Barreto AD. Stroke 2013; 44: 3376-3381


Conclusion: Thrpmbolysis with ultrasound
• Clot busting drug (systemic tPA)
- Hemostatic clot & tPA
• Sonothrombolysis
- Relatively safe & effective thrombolytic modality
- Combination of other modalities (MB, Catheter sono-injection)
• Benefits
- Sonothrombolysis & diagnostic value (eq. reocclusion)
• Limitations
- Timely need of sono-experienced person
- Lack of the expectation of complete recanalization
- Not suitable in ICAS occlusion (eq. more prevalent in Asian)