What Matters in the Results of Repeated Intravenous Thrombolysis for Recurrent Ischemic Stroke?

Jian Wu^a Qiang Huang^b Qing-feng Ma^c

^aDepartment of Neurology, Beijing Tsinghua Changgung Hospital, Beijing Tsinghua University, ^bDepartment of Neurology, Shijingshan Teaching Hospital of Capital Medical University, Beijing Shijingshan Hospital, and ^cDepartment of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China

Dear Sir,

We read with interest the article by Laible et al. [1] regarding repeated thrombolysis (RT) for acute ischemic stroke (AIS). Although this study has attempted to address the efficacy and safety issue of RT, we strongly feel that one should be cautious in understanding the conclusion. Since the data of onset-to-treatment time were not collected in 33.3% cases and the sample size was also small, the conclusion cannot be considered powerful and authentic.

We conducted a systemic literature review in PubMed up to December, 2015. A total of 15 studies [1–15] involving 57 cases and 61 RTs were collected. The details are shown in the (table 1). The median age was 73 at the first event, the median time inter-

val 225 days and 45.9% female. Heavier severity and worse functional outcome were observed in the RT group, but the difference of intracranial hemorrhages (ICHs) from 2 events did not reach statistical significance. More ICHs occurred in RTs with prior stroke within last 30 days than those in chronic stroke phase in a subgroup analysis (25.0–4.9%, $p = 0.018$). Only National Institutes of Health Stroke Scale (NIHSS) was significantly associated with a good functional outcome (OR 0.921, 95% CI 0.857–0.990) and ICH (OR 1.177, 95% CI 1.031–1.344) in the logistic regression analysis.

Our literature review indicated that baseline stroke severity was the main predictor of the functional outcome and ICH

after RT, similar to the results of the first thrombolysis in AIS [16, 17]. The accumulation of disability (measured by NIHSS) in recurrent stroke could have contributed to the worse prognosis after RT. We concluded that the results of RTs were mainly associated with baseline stroke severity, and RTs with recent stroke should be more cautious. That is, the new onset severity and time interval between 2 events should be considered when assessing the benefit/risk ratio of RT treatment.

Disclosure Statement

The authors declare no conflicts of interest.

Table 1. Patients with repeated intravenous thrombolysis for recurrent ischemic stroke

Author and reference	Case no	Age/sex	Cardiovascular risk factors	OTT in the 1st event, min	NIHSS in the 1st event	ICH	Good clinical outcome	Inter-thrombolysis interval, days	OTT in the 2nd event, min	NIHSS in the 2nd event	ICH	Good clinical outcome
Topakian et al. [2]	1	50/M	None	120	9	No	Yes*	4	85	10	No	Yes
Smadja et al. [3]	2	74/M	HTN	240	6	No	Yes*	0.25	60	22	Yes	Yes*
Sauer et al. [4]	3	62/F	NA	90	4	No	Yes	700	60	19	No	No
	4	84/F	NA	120	9	No	Yes	90	120	12	No	Yes
	5	76/M	NA	125	12	No	Yes	210	165	6	No	Yes
	6	71/M	NA	65	2	No	Yes	270	180	6	No	Yes
	7	81/F	NA	140	18	No	Yes	730	200	18	No	No
	8	62/M	NA	150	6	No	Yes	545	120	7	No	Yes
	9	53/F	NA	90	2	No	Yes	240	170	27	No	Yes
	10	64/F	NA	270	18	Yes	Yes	1,460	60	22	No	No
	11	62/M	NA	60	3	No	Yes	300	120	5	No	Yes
								790 (between 2nd and 3rd treatment)	140	7	No	Yes
Arsava et al. [5]	12	67/M	AF, BMVR	120	5	Yes	Yes	700	90	20	No	Yes
Nicoli et al. [6]	13	77/F	None	100	12	No	Yes*	7	95	7	No	Yes*
								10 (between 2nd and 3rd treatment)	105	10	No	Yes*
Cappellari et al. [7]	14	75/F	HTN, AF	175	4	No	Yes*	2	35	15	No	Yes*
Brigo et al. [8]	15	73/M	DM, HL	240	4	No	Yes*	2	60	12	No	Yes*
Alhazaa et al. [9]	16	81/F	AF	NA	NA	No	No*	6	NA	23	Yes	No
	17	83/M	CHD, smoking	NA	NA	No	Yes*	70	NA	9	No	No
	18	87/M	HTN, HL, CHD, smoking	NA	NA	No	Yes*	70	NA	4	No	Yes
Yoo et al. [10]	19	50/F	None	420	8	No	Yes*	6	72	18	No	Yes
	20	70/M	HTN	150	18	No	No	180	169	13	No	No
	21	73/F	DM	70	12	No	Yes	90	55	12	No	Yes
	22	74/F	HTN	120	7	No	Yes	485	125	22	No	Yes
	23	56/M	HTN, DM	316	15	No	Yes	2,310	300	15	No	Yes

Table 1. (continued)

Author and reference	Case no	Age/sex	Cardiovascular risk factors	OTT in the 1st event, min	NIHSS in the 1st event	ICH	Good clinical outcome	Inter-thrombolysis interval, days	OTT in the NIHSS 2nd event, min	ICH Good clinical outcome
	24	67/M	HTN, DM	70	6	No	Yes	1,430	67	No Yes
	25	75/F	HL	100	14	No	No	1,125	150	No No
	26	76/F	HTN, HL, AF, CHF	120	18	No	Yes*	4	240	Yes No
Sposato et al. [11]	27	69/M	Megadolichobasilar ectasia	180	7	No	Yes	365	120	No Yes
Cambron et al. [12]	28	73/M	HTN, HL	NA	NA	No	Yes*	6	NA	No Yes
Qureshi et al. [13]	29	54/M	None	NA	NA	No	Yes*	49	NA	No Yes
Mechtouff et al. [14]	30	42/M	Smoking	120	7	No	Yes	150	208	No Yes
								14 (between 2nd and 3rd treatment)	150	No Yes
								7 (between 3rd and 4th treatment)	90	No Yes
Laible et al. [1]	31	79/F	HTN in 18/24 cases; DM in 8/24 cases; AF in 6/24 cases	90	2	No	Yes	150	200	Yes No
	32	71/M		100	13	No	Yes	105	120	No Yes
	33	80/M		NA	19	No	Yes*	30	420	No No
	34	68/M		180	9	No	No	910	180	No No
	35	76/M		120	5	No	Yes	1,335	90	No No
	36	57/F		60	11	No	Yes	4,025	150	Yes No
	37	59/M		100	10	No	Yes	120	87	No Yes
	38	74/M		150	12	No	Yes	700	70	No Yes
	39	85/M		NA	NA	No	Yes	475	90	No No
	40	80/F		180	6	No	Yes	123	180	No Yes
	41	65/M		120	9	No	Yes	1,550	110	No No
	42	75/F		NA	12	No	Yes	790	90	No No
	43	63/M		165	7	No	No	288	NA	No No
	44	87/F		55	8	No	Yes	1,365	80	No No
	45	75/F		135	8	No	No	2,160	125	No No

Table 1. (continued)

Author and reference	Case no	Age/sex	Cardiovascular risk factors	OTT in the 1st event, min	NIHSS in the 1st event	ICH	Good clinical outcome	Inter-thrombolysis interval, days	OTT in the 2nd event, min	NIHSS in the 2nd event	ICH	Good clinical outcome
	46	81/F		107	1	No	Yes	270	120	2	No	Yes
	47	61/M		NA	18	No	Yes	940	360	15	No	Yes
	48	87/F		135	12	No	No	138	150	14	No	No
	49	80/F		NA	7	No	No	117	NA	15	No	No
	50	51/F		350	11	No	No*	73	119	14	No	No
	51	74/M		82	11	No	Yes	270	165	6	No	Yes
	52	48M		NA	2	No	Yes*	66	220	2	No	Yes
	53	87/F		115	4	No	Yes	635	130	27	No	No
	54	73/F		85	10	No	Yes	404	NA	0	No	Yes
Huang et al. [15]	55	72/F	CHD, AF	300	5	No	Yes	225	240	11	No	Yes
	56	50/M	HTN	205	4	No	Yes	1,140	120	6	No	Yes
	57	53/F	HTN, CHD	233	4	No	Yes	169	210	4	No	Yes

OTT = Onset-to-treatment time; M = male; F = female; HTN = hypertension; NA = not available; AF = atrial fibrillation; BMVR = bioprosthetic mitral valve replacement; DM = diabetes mellitus; CHF = congestive heart failure; HL = hyperlipidemia; CHD = coronary heart disease.

Good clinical outcome was defined as significant progress in NIHSS (≥ 4) at discharge when * was indicated, and others were defined as modified Rankin Scale ≤ 2 at 3 months.

References

- 1 Laible M, Jenetzky E, Möhlenbruch M, Ringleb PA, Rizos T: Repeated intravenous treatment with recombinant tissue-type plasminogen activator in patients with acute ischemic stroke. *Eur Neurol* 2015;74:127–134.
- 2 Topakian R, Gruber F, Fellner FA, Haring HP, Aichner FT: Thrombolysis beyond the guidelines: two treatments in one subject within 90 hours based on a modified magnetic resonance imaging brain clock concept. *Stroke* 2005;36:e162–e164.
- 3 Smadja D, Olindo S, Saint-Vil M, Chausson N: Sequential combination of two intravenous thrombolytics (recombinant tissue plasminogen activator/tenecteplase) in a patient with stroke and cardioembolic basilar artery occlusion. *J Stroke Cerebrovasc Dis* 2009;18:68–71.
- 4 Sauer R, Huttner HB, Breuer L, Engelhorn T, Schellinger PD, Schwab S, Köhrmann M: Repeated thrombolysis for chronologically separated ischemic strokes: a case series. *Stroke* 2010;41:1829–1832.
- 5 Arsava EM, Topcuoglu MA: De-novo thrombolysis for recurrent stroke in a patient with prior history of thrombolysis. *Blood Coagul Fibrinolysis* 2010;21:605–607.
- 6 Nicoli F, Faivre A, Squarcioni C, Combaz X, Girard N: Repeated MR-based intravenous thrombolysis in a patient with short interval stroke recurrences. *J Neuroradiol* 2011;38:256–258.
- 7 Cappellari M, Tomelleri G, Carletti M, Bovi P, Moretto G: Intravenous thrombolysis on early recurrent cardioembolic stroke: ‘Dr Jekyll’ or ‘Mr Hyde’? *Blood Coagul Fibrinolysis* 2012;23:78–81.
- 8 Brigo F, Bovi T, Tomelleri G, Bovi P, Moretto G: Repeated systemic thrombolysis after early recurrent stroke: always hazardous? *Can J Neurol Sci* 2012;39:114–116.
- 9 Alhazaa M, Sharma M, Blacquièrè D, Stotts G, Hogan M, Dowlatshahi D: Thrombolysis despite recent stroke: a case series. *Stroke* 2013;44:1736–1738.
- 10 Yoo HS, Kim YD, Lee HS, Song D, Song TJ, Kim BM, Kim DJ, Kim DI, Heo JH, Nam HS: Repeated thrombolytic therapy in patients with recurrent acute ischemic stroke. *J Stroke* 2013;15:182–188.
- 11 Sposato LA, Salutto V, Beratti DE, Monti P, Riccio PM, Mazia C: Adverse outcome of early recurrent ischemic stroke secondary to atrial fibrillation after repeated systemic thrombolysis. *Case Rep Vasc Med* 2013;2013:371642.
- 12 Cambron M, Van Hooff RJ, Nieboer K, De Keyser J, Brouns R: Successful repetitive intravenous thrombolysis in a patient with recurrent brainstem infarctions due to megadolichobasilar ectasia. *Jama Neurol* 2013;70:520–521.
- 13 Qureshi AI, Malik AA, Freese M, Thompson MJ, Khan AA, Suri MF: Readministration of intravenous alteplase in acute ischemic stroke patients: case series and systematic review. *Am J Emerg Med* 2015;33:307.e1–e4.
- 14 Mechtouff L, Ritzenthaler T, Cho TH, Derex L, Feugier P, Berthezene Y, Collet-Benzaquen D, Douek PC, Nighoghossian N: High-resolution MRI: detection of a culprit plaque after recurrent thrombolysis. *J Neurol* 2015;262:2773–2775.
- 15 Huang Q, Ma QF, Feng J, Cheng WY, Jia JP, Song HQ, Chang H, Wu J: Factors associated with In-Hospital delay in intravenous thrombolysis for acute ischemic stroke: lessons from china. *PLOS One* 2015;10:e0143145.
- 16 Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivet JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, Del Zoppo GJ, Baigent C, Sandercock P, Hacke W; Stroke Thrombolysis Trialists’ Collaborative Group: Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929–1935.
- 17 Jickling GC, Liu D, Stamova B, Ander BP, Zhan X, Lu A, Sharp FR: Hemorrhagic transformation after ischemic stroke in animals and humans. *J Cereb Blood Flow Metab* 2014;34:185–199.