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Low-dose intravenous tissue plasminogen activator for acute ischaemic stroke: an alternative or a new standard?

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ABSTRACT

Background: With the recent publication of a large clinical trial on the use of a lower dose of intravenous (IV) tissue plasminogen activator (tPA) for acute ischaemic stroke (AIS), the concept of using a different dose has been debated. We intend to review the literature on using a lower dose of IV tPA and gain a better understanding of the impact of different IV doses on the treatment of patients with AIS.

Methods: A comprehensive literature search of the related topics in PubMed, EMBASE, Web of Science and MEDLINE was carried out. Key words used include low dose IV tPA, thrombolysis, Alteplace and tPA for AIS. Findings were tabulated according to the size of the cohort studied, outcome, adverse event and level of evidence. The results of all studies using lower doses were analysed for efficacy and adverse events.

Results: From 1992 to 2016, there were 23 trials that included 10 950 patients published on the use of lower doses of IV tPA for AIS. Doses ranged from 0.5, 0.6, 0.75 to 0.85 mg/kg. Most were observational, retrospective and registry studies. One was a prospective open-label randomised controlled trial. 13 trials combined lower doses of IV tPA with a glycoprotein IIb/IIIa inhibitor or thrombectomy. Patients treated with lower doses of IV tPA showed a trend of lower rate of symptomatic intracranial haemorrhage and mortality at 3 months but slightly more disability.

Conclusions: Lower doses of IV tPA showed less haemorrhagic events but were not more effective compared with the standard dose. The optimal low dose of IV tPA remains unclear. Patients with AIS with a high risk of developing sypmtomatic intracranial haemorrhage might benefit from lower dose IV tPA, such as 0.6 mg/kg.

INTRODUCTION

Stroke is one of the leading causes of disability and death in developing countries, especially in China.[1 2] Intravenous (IV) tissue plasminogen activator (tPA; 0.9 mg/kg) is the only proven effective medical treatment for acute ischaemic stroke (AIS) during the past 20 years.[3–5] However, there is still a controversy on what the optimal doses of IV tPA should be. Many neurologists in Asia consider that lower doses of IV tPA are better for Asian patients with stroke because of the racial difference in coagulation and fibrinolysis responses.[6–8] Many observational and registry studies have been conducted in order to prove the efficacy and safety of lower doses of IV tPA. Consequently, Japan is the only nation that recommends 0.6 mg/kg of IV tPA in its stroke care guideline.[9] The newly published low-dose versus standard-dose tPA in the ENhanced Control of Hypertension and Thrombolysis strokE stuDy (ENCHANTED) has helped resolve the low-dose controversy to some extent but also raised more concerns.[10] In order to help clinicians decipher through this rather complex issue, we performed an up-to-date overview of lower doses of IV tPA for AIS.

METHODS

Using key words 'low dose IV tPA', 'thrombolysis', 'Alteplace' and 'tPA' plus 'acute ischemic stroke' and 'cerebral infarction', related literatures were searched in PubMed, EMBASE, Web of Science and MEDLINE between 1992 and May 2016 in order to identify any related clinical studies. All published trials have been included in the analysis while review type articles were excluded. Level of evidence and grades of recommendation were assigned to each of these trials based on the standard.[11] Results from these trials were tabulated and compared.

RESULTS

From 1992 to May 2016, 24 trials including 11 127 patients on the use of lower doses of IV tPA for AIS were identified. Doses ranged

from 0.5, 0.6, 0.75 to 0.85 mg/kg. Most studies were observational, retrospective and of registry type (table 1). Only one study was a prospective randomised, open-label controlled trial.

Two trials combined lower doses of IV tPA with a glycoprotein IIb/IIIa inhibitor (table 2). Eight trials tested low-dose IV tPA combined with intra-arterial (IA) thrombolysis or thrombectomy.

Early-dose escalation studies

Two pilot dose escalation studies by Brott *et al*[3] and Haley *et al*[4] were the basis for the decision on the standard dose of IV tPA at 0.9 mg/kg.[5] In the first pilot study, doses of 0.35 mg/kg (n=6), 0.60 mg/kg (n=12), 0.85 mg/kg (n=30), 0.95 mg/kg (n=25) and 1.08 mg/kg (n=1) were used within 90 min of symptom onset in patients with AIS between 18 and 80 years of age.[3] The study demonstrated that patients treated with 0.85 mg/kg were more likely to achieve better neurological improvement at 24 hours compared with patients treated with 0.6 mg/kg.[3] No sypmtomatic intracranial haemorrhage (sICH) was observed when doses of ≤0.85 mg/kg were used.[3] The second study tested doses of 0.6 mg/kg (n=8), 0.85 mg/kg (n=6) and 0.95 mg/kg (n=6) in patients with AIS presenting within 90–180 min after symptom onset.[4] Two higher dose tiers had sICH (17% in doses of ≥0.85 mg/kg).[4] Efficacy at a lower dose of IV tPA in these pilot trials was not examined. The optimal doses of IV tPA were still inconclusive.[3 4] The major concern about tPA remained to be the factors related to sICH.[12]

Low-dose IV tPA studies in Asians

Japan has conducted many low-dose IV tPA trials and all of them were single-arm observational studies.[6 9 13] The rationale for the Japanese to decide on recommending 0.6 mg/kg instead of 0.9 mg/kg was based on a dose-range study of duteplase completed two decades ago[14] which showed that the lower dose was optimal for patients with AIS up to 6 hours after onset. Since 2005, 0.6 mg/kg has been the only approved dosage given for patients with AIS within 3 hours of onset in Japan.[6] This recommendation was based on the results of the Japanese thrombolysis study which suggested clinical benefits.[6] Subsequent studies, the Japan Alteplase Clinical Trial 2 and Japan post-Marketing tPA Registration Study, also demonstrated both efficacy and safety with the 0.6 mg/kg dose.[9 13] In the Japan Alteplase Clinical Trial 2, the dose of tPA was 0.6 mg/kg and the vascular outcome was evaluated by MR angiogram (MRA) at 6 and 24 hours after symptom onset.[13] Recanalisation was noted on MRA in 51.7% of patients at 6 hours and in 69.0% of patients at 24 hours after symptom onset. In total, 46.6% of patients achieved favourable clinical outcome (modified Rankin scale (mRS) score of 0–1 at 3 months after onset) with no sICH.[13] The Japan post-Marketing tPA Registration Study enrolled 7492 patients in 942 centres. The primary purpose was to investigate whether 0.6 mg/kg IV tPA could be safe and effective in routine clinical practice for Japanese patients.[9] The study demonstrated 33% of favourable outcome in the efficacy analysis of 4944 patients. In the safety analysis of 7492 patients, the incidence of sICH was 3.5% within 36 hours and the overall mortality rate was 13.1%.[9]

In Singapore, a local institution used 0.9 mg/kg to calculate the total dose but capped the maximum dose at 50 mg in order to avoid sICH and reduce the cost of tPA. There was no sICH at 18 months of follow-up but the rate of functional independence was low.[15] It changed its protocol and used the standard dose. This change has improved the efficacy from 35% to 59% (p=0.011), with a decreased rate of sICH from 14.5% to 1.2% (p=0.004).[15]

In contrast, in a small sample Vietnamese study, patients treated with low-dose IV tPA were more likely to achieve functional independence at 3 months (56.3% vs 34.2%; p=0.01) and only 2.1% of patients had sICH in the low-dose group, compared with those who received the standard dose.[16]

In the Korean national registry study, low-dose IV tPA was given to 450 patients (29.5%) and standard-dose tPA to 1076 patients (70.5%).[17] Low-dose therapy was comparable to standard-dose therapy when measured by the 3-month mRS score (OR 0.95, 95% CI 0.68 to 1.32) and mortality (OR 0.54, 95% CI 0.35 to 0.83).[18] However, the incidence of sICH in the low-dose group was 8.4%, compared with 6.4% in the standard-dose group.[18]

In the Chinese population, Taiwan Thrombolytic Therapy for Acute Ischemic Stroke demonstrated that the standard dose of IV tPA might not be optimal to treat older Chinese patients.[19] Researchers used the Safe Implementation of Thrombolysis in Stroke: a Monitoring Study of Safety and Efficacy of Thrombolysis in Stroke (SITS-MOST) criteria and recruited 241 participants. Among them, 116 had low doses (0.72±0.07) and 125 received the standard dose (0.9 mg/kg), respectively. The lower dose group demonstrated a higher percentage (41.4%) of functional independence (mRS score 0–1) in all age groups.[19] For patients older than 70, 53.6% in the lower dose group had functional independence versus 32.6% in the standard-dose group.[19] The investigators found that patients receiving a standard dose had a twofold risk of sICH (8.0% vs 2.6%) and a higher rate of mortality within 3 months (12.8% vs 6.9%).[17] Hence, there was a trend that low-dose tPA seemed to be safer in elderly patients. However, in another Taiwan-based study, Chen *et al*[20] recruited 261 patients in a retrospective study involving two centres. Among them, 105 received 0.7 mg/kg IV tPA and 156 had 0.9 mg/kg. The study demonstrated no difference between the two dose groups on outcome at 3 months (38.4% and 41.1%, respectively; p=0.676).[20] There was no difference in the occurrence of sICH in the standard-dose group compared with the low-dose group (2.6% vs 4.8%, p=0.34).[20] In a larger national

Table 1 The efficacy and safety of low-dose tPA treatment in acute stroke

Author	Year	Design	Sample Size	Racial	Age mean ±SD, median (IQR)	Baseline NIHSS mean±SD, median (IQR)	Time window (hour)	Dosage (mg/kg)	FO	sICH (%)	Mortality	Level of evidence
Anderson	2016	RCT	1654	1043/1651 Asian	68 (58–76)	8 (5–14)	4.5	0.6	46.8	5.9	53.2	A
Morihara	2016	Retrospectively	121	Japanese	74.6±10.3	11 (6–18)	3	0.6	36.0	2.5	6.9	C
			56	Japanese	75.7±11.7	12 (6.75–18)	3–4.5	0.6	23.4	3.6	8.3	C
Kim	2015	Retrospective	450	Korean	69.0±12.7	13.9±7.0; 15 ([8–19])	4.5	0.6	32.4	8.4	12.7	C
Liao	2014	Registry	75	Chinese	62 (52–71)	10 (7–17)	4.5	0.5–0.7	41.9	0	5.4	B
			131		68 (57–73)	10 (6–15)		0.7–0.85	48.0	8.7	8.66	
Pan	2013	Observational	31	Chinese	63.8±9.3	8.7±4.6	3	<0.75	51.5	3	3.2	C
			33		64.5±7.7	9.2±5.0	3	0.75–0.90	61.2	9.7	3	
Chen	2012	Registry	105	Taiwan	67.9±12.8	13.3±6.2	3	0.7 (0.66–0.74)	41.1	4.8	7.6	B
Zhou	2010	Observational	23	Chinese	69.8±8.6	12.6±6.8	4.5	0.6–0.7	34.8	4.3	17.4	C
			31		72.9±8.7	12.7±5.0	4.5	0.8	38.7	3.2	16.1	
Chao	2010	Retrospective	116	Taiwan	66.7±13.3	14.9±6.0	3	0.72±0.07	39.3	5.4	10	C
Nguyen	2010	Prospective	48	Vietnamese	57 (18–78)	12 (5–23)	3	0.62 (0.6–0.86)	56.3	2.1	2.1	B
Sharma	2010	Retrospective	48	Multiethnic in Asian	55±12	12 (10)	3	0.9, maximum 50mg	0.35	0.058	0.1	C
Nakagawara	2010	Observational	7492	Japanese	72 (65–79)	15 (9–20)	3	0.6	0.33	0.044	13.2	B
Mori	2010	Observational	58	Japanese	70.3±11.5	12 (5–22)	3	0.6	0.466	0	1.7	C
Yamaguchi	2006	Prospective	103	Japanese	70.9±9.8	15 (5–30)	3	0.6	36.9	5.8	0.097	B
Haley	1992	Pilot	8	1/8 black	74 (72–76)	14.5 (9–17)	3	0.6	NA	12.5	25	C
			6	1/6 Asian	71 (67–75)	23.5 (23–24)	3	0.85		33.3	50	
			6	2/5 black	66.5 (66–67)	18 (12–22)	3	0.95		37.5	16.7	

Level of evidence was assessed according to American Heart Association/American Stroke Association (AHA/ASA) criteria.
FO, favourable outcome at 3 months follow-up; NA, not available; NIHSS, National Institution of Health Stroke Scale; RCT, randomised controlled trial; sICH, symptomatic intracranial haemorrhage, refer to National Institute of Neurological Disorders And Stroke Recombinant Tissue Plasminogen Activator Stroke Study (NINDS) criteria; tPA, tissue plasminogen activator.

Table 2 Summary of standard dosage versus the combination of other treatment plus low-dose tPA

Author	Year	Racial (% black)	Sample	Age (IQR)	Baseline NIHSS (IQR)	Time window (hour)	Dosage (mg/kg)	Other	Control 0.9 mg/kg/L	Favourable outcome (%)*	sICH (%)	Mortality
Morihara	2016	Japanese	21	71.7	10 (6–16)	<4.5	0.6					
Opeolu[39]	2015	13	85	68 (33–86)	11 (6–31)	2	0.6	Eptifibatide	0.9	52	0	15.3
Adeoye												
Pancioli	2013	13.9	101	71.6 (58.1–81.5)	19	<4.5	0.6	Eptifibatide	0.9	43.6	2	19.8
Pancioli	2008	NA	29	72.7 (67–77	14.0 (10–20)	<3	0.3	Eptifibatide	0.9	31.0	3	28.0
			40	68.0 (52–77)	13.5 (8–17)	<3	0.45	Eptifibatide	0.9	30.0	0	18.0
IMS II	2007	11.1	81	64±11.5†	19	<3	0.6	IA thromolysis +EKOS system	NA	33.0	9.9	16.0

*Favourable outcome indicates modified Rankin scale 0–1 at 3 months follow-up.
†Only mean±SD were available.
IA, intra-arterial; IMS, Interventional Management of Stroke; NA, not available; NIHSS, National Institution of Health Stroke Scale; sICH, symptomatic intracranial haemorrhage, refer to NINDS criteria; tPA, tissue plasminogen activator.

registry study in the Chinese population, the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China enrolled over 900 patients. The authors concluded that standard-dose IV tPA increased the chance of achieving a favourable outcome without increasing the risk of sICH compared with low-dose IV tPA.[21] Therefore, in Chinese patients with AIS treated with low-dose tPA, the rate of sICH was 4.6% (28/544) and the rate of mortality at 90 days was 8.1% (44/540). The rate of favourable outcome was 43.8% (232/530). Compared with other Asian ethnic groups, the Chinese and Korean populations had a higher incidence of sICH (4.6% and 8.4% respectively, vs 0–3.5%) without increased mortality.[21]

The combination of low dose or standard dose of IV tPA with other treatment modalities for AIS

Several studies have explored the combination of low dose or standard dose of IV tPA plus IA tPA,[22–29] including one with IA thrombectomy study[30] and two with a glycoprotein IIb/IIIa agent.[31 32] IV therapy was usually given prior to other treatments. The rationale of using 0.6 mg/kg of IV tPA prior to endovascular treatment was to avoid using a total dose higher than 0.9 mg/kg of tPA.[33] In the Interventional Management of Stroke (IMS) III trial, patients randomised to endovascular treatment were administered IV tPA at 0.6 mg/kg (bolus and infusion) followed by an IA dose of 0–22 mg. The total tPA dose was kept to <0.9 mg/kg.[29] The steady-state concentration of 2.5 µg/mL was achieved with an IV tPA dose of 0.75 mg/kg.[27] Therefore, the effective steady state of the concentration of IV tPA may not always be the same with the standard dose or lower doses. Analysis of the relationship between total (IV+IA) dose of tPA and risk of sICH in the IMS II trials did not demonstrate the same safety threshold as seen in pilot trials with IV tPA.[33] The IV dose in the combined arm was increased from 0.6 to 0.9 mg/kg and a combined maximum IV and IA total dose of 112 mg was defined as the maximum dose in the IMS III trial.[29] IMS III was terminated due to futility issues and no outcome was generated.[29] A systematic review of 11 trials was conducted to compare IV low-dose tPA versus standard doses before endovascular treatment.[34] sICH was seen in 26 (8%) patients in the 0.6 mg/kg group compared with 10 (7%) in the 0.9 mg/kg group.[33] Patients in the 0.9 mg/kg group had a higher rate of favourable outcome but a similar rate of sICH. Depending on the statistical methods used, the difference in angiographically identified recanalisation between 0.9 and 0.6 mg/kg IV tPA was rated as significant (p=0.03, events/trial syntax logistic regression) or borderline significant (p=0.07, random-effects model).[33] However, a recent meta-analysis on endovascular thrombectomy after large vessel ischaemic stroke only included full-dose tPA.[35] There is no direct comparison between low-dose and full-dose tPA in thrombectomy studies using a new generation of devices.

The ENCHANTED trial

Low-dose versus standard-dose tPA in the ENCHANTED was the first multicentre and multinational randomised prospective open-label study which compared 0.9 to 0.6 mg/kg IV tPA for patients with AIS within 4.5 hours of onset.[10] Patients who received the low-dose (0.6 mg/kg) IV tPA were given 15% of the total dose as IV bolus followed by 85% of the total dose as infusion over 1 hour. The control group with the standard dose of IV tPA (0.9 mg/kg) was given 10% of dose as IV bolus followed by 90% of dose as IV infusion over 1 hour.[10] It was designed as a non-inferiority trial with the primary outcome to be the rate of combined disability and death (mRS 2–6) at 90 days, and secondary outcome to be the rate of sICHs. Non-inferiority was prespecified as an upper limit for non-inferiority of 1.14, which was derived from a published Cochrane meta-analysis of IV tPA.[10 36] A total of 3310 patients from 111 centres in 13 countries were recruited and 3206 patients were entered into the analysis with 64% Asians. Among them, 20.6% had lacunar stroke and 14% were elderly patients older than 80. The primary outcome of the trial was not reached and the authors concluded that the trial did not show the non-inferiority of low-dose tPA to standard-dose tPA with respect to death and disability at 90 days.[10] Despite the statistical failure, the trial showed that low-dose tPA was non-inferior to the standard dose in the ordinal analysis of mRS scores (unadjusted common OR 1.00; 95% CI 0.89 to 1.13; p=0.04 for non-inferiority) and less major sICH occurred in the low-dose group (1.0% vs 2.1%, p=0.01); fatal events occurred less within 7 days (0.5% vs1.5%, p=0.01). Mortality at 90 days did not differ significantly between the two groups (8.5% and 10.3%, respectively; p=0.07). However, patients receiving a low dose had a higher rate of disability measured by mRS scores between 2 and 5.

DISCUSSION

There were several concerns of the ENCHANTED trials. Since it was an open-label trial, many biases could not be avoided. The publication did not clarify whether patients were enrolled consecutively, which could also bring bias. The follow-up, done by either a face-to-face in-person visit or telephone interview, would bring variable assessment and inaccurate results. There are also some concerns about the authors of the study since they had significant conflicts of interest. From the trial design point of view, low-dose IV tPA did not meet the upper limit of the prespecified non-inferiority threshold for the OR in comparison to standard-dose tPA for the primary outcome of death or disability at 90 days. The combined primary outcome of death and disability masked the higher disability rate in the low-dose group. Finally, this study did not prove non-inferiority of low-dose IV tPA and did not show superiority to the standard dose of IV tPA either.[37]

Despite these concerns, ENCHANTED performed well. It was one of the trials which showed that statistical hypothesis testing would not match the clinical performances. Had the primary outcome was designed as mortality rate, then 0.6 mg/kg would be superior since this dose caused less death and less fatal ICH. Patients treated with low dose have worse outcome assessed by mRS of 1–5, which meant more moderate-to-severe disability. If Asians and non-Asians are analysed separately, non-Asians performed better when measured in the mRS range of 4–6. Furthermore, the trial showed that significantly fewer sICHs in patients received 0.6 mg/kg.

Finally, the ENCHANTED trial, which was the largest trial of its kind until now, confirmed that 0.6 mg/kg IV tPA had a better safety profile but failed in non-inferior comparison in efficacy as designed.[10]

As we are reviewing the data, the THrombolysis for Acute Wake-up and unclear-onset Strokes trial has been ongoing. It aims to determine the efficacy and safety of IV alteplase at 0·6 mg/kg but uses MRI to select patients with AIS who presented with unclear time of symptom onset.[38] Perhaps this trial can provide the needed evidence that patients with wake-up stroke could benefit from low-dose IV tPA.

On the basis of this review, some subgroups of patients with AIS might be benefited from the 0.6 mg/kg dose, for example, elderly patients, patients with relatively high blood pressure at baseline, patients with cardioembolism, patients with old ischaemic stroke, patients on multiple antiplatelet agents or anticoagulants.[10] The benefit of these subgroups was supported by other studies. A Chinese population study showed that the elderly might benefit more in the low-dose group.[19] In addition, the Japanese postmarket observational study with a large proportion of elderly patients with cardioembolism revealed a remarkably favourable outcome, which is nearly the same rate as that seen in another standard-dose observational study.[10] Other subgroups of patient, potentially to be optimal with low dose, may include on antithrombotics with early signs of larger ischemic infarction on CT and with severe stroke (National Institution of Health Stroke Scale (NIHSS) >12). Further studies are still needed to confirm the benefit in safety in these population. In patients who need bridging therapy, IV low-dose tPA could be an option, although a majority of the newly published IV tPA plus IA thrombectomy studies used the standard dose of IV tPA.[29 30 33 35] Therefore, for those with severe strokes and identified large vessel occlusions, a standard dose of IV tPA should be considered before IA thrombectomy.

The ENCHANTED trial included patients within 4.5 hours of onset in both dose groups. In European Cooperative Acute Stroke Study (ECASS) III trials, those who were older than 80, with a history or stroke and diabetes and anticoagulation, had worse outcome. Perhaps in these patients now excluded based on ECASS III results, 0.6 mg/kg might be beneficial. Other studies also supported the use of a lower dose in this patient population.[10 36 37] Based on this comprehensive review,

it is rather clear that low-dose IV tPA can lower the incidence of sICH. However, it is unclear if a lower dose would offer the same efficacy as standard dosage in selected patients based on this review.

Last but not the least, low-dose IV tPA (a single 50 mg vial of Actilyse, Boehringer Ingelheim) could become a preferred option for patients who cannot afford the full dose in certain areas of the world.

CONCLUSION

Although the level of evidence was not high, studies prior to the ENCHANTED trial have shown that low-dose IV tPA was associated with a lower rate of sICH and effective in treating patients with AIS.[10] Despite some controversy, the ENCHANTED trial has confirmed the lower rate of sICH with 0.6 mg/kg of IV tPA.[10] However, the 0.6 mg/kg dose group was associated with a high incidence of moderate-to-severe disability and did not achieve the primary outcome as predetermined statistically. Since the mortality rate in both groups was similar, the increased rate of moderate disability was partially balanced by the lower rate of sICH. Beside 0.6 mg/kg, other low doses of IV tPA have not been well studied. In many developing countries in Asia such as China, a low dose provided an attractive option since it would lower the cost and help to overcome the underuse of IV tPA. The strategy of IV tPA dosage should depend on the patient's clinical profile, financial condition and a clear understanding of the current evidence. Standard dose should be considered first, but 0.6 mg/kg may be an option in certain subgroups. The practising physicians should take into the consideration that patients who received 0.6 mg/kg IV tPA are more likely to be alive at 7 days and with a low chance of developing sICH, but with a higher chance of having moderate disability.

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