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Thrombolysis with Low-Dose *Versus* Standard-Dose Alteplase in 4.5 Hours After Acute Ischemic Stroke; A Four-Months Prospective Study

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1. Abstract

Background: In Japan, Pakistan and Vietnam, 0.6 mg of Alteplase per kilogram body weight within 3 hours was approved for standard guideline, although the safety and efficacy in acute ischemic stroke within 4.5 hours has not been established. We conducted four-month prospective study to compare the safety and efficacy of 0.6 mg, 0.75 mg and 0.9 mg of Alteplase per kilogram body weight.

Methods: In cohort A, the patients were randomly assigned to receive intravenous 0.6 mg or 0.75 mg or 0.9 mg of Alteplase per kilogram body weight in a 1:1:1. Interim analysis was performed after complete cohort A. In cohort B, patients were assigned to receive 0.9 mg of Alteplase per kilogram body weight (standard-dose). The primary end points were death, favorable outcome at discharge and 90-day and intra-cerebral hemorrhage. The secondary end points were good outcomes, Improved mRS at discharged and 90-day, number of patients with length of hospital stay <7 days and overall complications.

Results: In Cohort A, 78 were randomly assigned to receive 0.6 mg or 0.75 mg (low-dose) or 0.9 mg of intravenous Alteplase per kilogram body weight. Less patients had favorable outcomes in 0.6 mg and 7.5 mg than 0.9 mg of Alteplase per kilogram body weight at discharge (P=0.0004) and at 90-day (P=0.05). In Cohort B, 330 were assigned to receive standard-dose Alteplase. Finally, 408 patients were enrolled with median time of Alteplase administration by 2 hours 49 min. There was no different onset to needle and death between low-dose and standard-dose Alteplase (P=0.82 and P=0.85). Less patients had favorable outcome and intra-cerebral hemorrhage with low-dose than standard-dose Alteplase (favorable outcomes: Relative risk (RR), 1.18; 95% confidence interval (CI), 1.09 to 1.27; P <0.001 at discharge and RR, 1.25; 95%CI, 1.07 to 1.46; P=0.003 at 90 day, intra-cerebral hemorrhage: RR, 0.05; 95%CI, 0.00 to 0.95; P=0.04. Less patients had improved modified Rankin Scale [mRS] at 90-day with low-dose than standard-dose Alteplase (RR, 1.66; 95%CI, 1.22 to 2.25; P=0.001; especially in the patients with initial systolic blood pressure <180 mmHg ; RR, 1.86; 95%CI, 1.35 to 2.56; P=0.0001). In patients with initial systolic blood pressure >180 mmHg, low-dose Alteplase group had more patients with mRS of 0-3 at 90-day and less patients with of mRS 4-6 at 90-day

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than standard-dose Alteplase (P=0.002). There was no significant different in length of stay and overall complications with low-dose than standard-dose Alteplase (P=0.15).

Conclusion: As compared with standard-dose, intravenous low-dose Alteplase administered within 4.5 hours after the onset of stroke significant less favorable outcome, intra-cerebral hemorrhage, but not different in death, especially in the patients with initial systolic blood pressure <180 mmHg. However, patients with initial systolic blood pressure >180 mmHg, intravenous low-dose Alteplase had less patients with disability and death and more patient's recovery with mRS of 0-3 at 90-day. (ClinicalTrial.gov Number, NCT03847883).

2. Keywords: Alteplase; Thrombolysis; Acute ischemic stroke; Recombinant tissue plasminogen activator; Low-dose Alteplase

3. Introduction

Acute ischemic stroke, the leading cause of death worldwide, presented rapidly developed signs/symptoms of acute limb/facial weakness, difficult speech, numbness, other neurovascular symptoms, lasting 24 hours, confirmed by neurological imaging with the relevant vascular infarction of the brain. The National Institute of Neurological Disorders and Stroke (NINDS), the European Cooperative Acute Stroke Study (ECASS) and the Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS) study demonstrated 0.9 mg of Alteplase per kilogram body weight administered within 3 hours to 4.5 hours after stroke onset improved functional recovery at 90-day [1-6]. Intravenous thrombolytic treatment with Alteplase is the standard treatment worldwide. In European countries, 0.9 mg of Alteplase per kilogram body weight is the standard-dosage recommendation. In Japan, Pakistan and Vietnam, 0.6 mg of Alteplase per kilogram body weight is recommendation for treatment of acute ischemic stroke within 3 hours, without clear established safety and efficacy in death, disability outcomes, irrespective of age, race, ethnicity and neurological severity in Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) [7].

In 2004, a meta-analysis of the NINDS, ECASS I and II, and ATLANTIS studies demonstrated the odds ratio of a favorable 90-day outcome increased as onset to treatment time. Only the time of stroke onset during wakefulness with stroke symptoms, less than 3 hours to 4.5 hours and National Institute of Health Stroke Scale (NIHSS) of 6-26, were the most important factor to determine the decision of standard-dose Alteplase [8]. Previous prospective multicenter nation-wild study in 2008-2012 established limitation access to complete data of acute ischemic stroke care interventions especially thrombolysis outcomes in Thailand. In 2012, national guideline of Thailand recommends 0.9 mg of Alteplase per kilogram body weight as the standard treatment. Most of previous studies demonstrated poor outcomes in the patients with high initial NIHSS, old aged, female gender, in-hospital complications, history of hypertension and permanent high blood glucose after treatment [9-12].

To establish the efficacy and safety of low-dose *versus* standard-dose Alteplase in 4.5 hours after acute ischemic stroke, we conducted a four-months prospective study in Lampang Hospital between October 2011 to March 2018.

4. Method

Eligible patients with fulfill the inclusion criteria without any exclusion criteria (Table 1), were performed computerized tomographic scan (CT) of the brain After signed informed consent and initial NIHSS assessment, a 15-item scale that measures the level of neurological impairment, range from 0 to 42 with higher value represent severe cerebral infarction. Patients with onset to needle <3.0 hours and NIHSS≥6 and patients with onset to needle 3.0 hours to 4.5 hours with NIHSS≥6 and ≤25 will be eligible for Alteplase (Actilyse; Boehringer Ingelheim),

lipophilized powder in sterile water for injection, divided into 10% of total dose was administered as a bolus intravenously and remained 90% of total dose was given by continuous intravenous infusion over a period of 60 minutes at emergency department.

Table 1: Major Inclusion and Exclusion Criteria.

Main inclusion criteria
Acute ischemic stroke
Age, 18 to 80 years
Onset of stroke symptoms up to 4.5 hours before initiation of Alteplase administration
Stroke symptoms present for at least 30 minutes with no significant improvement before treatment
NIHSS ≥6
Main exclusion criteria
NIHSS >25 if onset to needle ≥3.0 Hours or stroke onset >4.5 hours
Intracranial hemorrhage
Time of symptom onset unknown
Symptoms rapidly improving or only minor before start of infusion
Seizure at the onset of stroke
Stroke or serious head trauma within the previous 90-day
Administration of heparin within the 48 hours preceding the onset of stroke, with an activate
Partial-thromboplastin time at presentation exceeding the upper limit of the normal range
Platelet count of less than 100,000 per cubic millimeter
Systole pressure greater than 185 mm Hg or diastole pressure greater than 110 mm Hg, or aggressive treatment intravenous medication) necessary to reduce blood pressure to these limits
Blood glucose less than 50 mg per deciliter or greater than 400 mg per deciliter
Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal Oral anticoagulant treatment
Major surgery or severe trauma within the previous 90-day
Other major disorders associated with an increased risk of bleeding

All patients were close monitored the blood pressure, oxygenation and heart rate in stroke unit, intravenous Nicardipine administration in all patients who had systolic blood pressure more than 185 mmHg to keep systolic blood pressure less than 180 mmHg before Alteplase administration. Follow up CT scan of the brain and follow up NIHSS assessment were performed at 24 hours. Repeated CT scan of the brain at 36 hours was performed in the patients who had intra-cerebral hemorrhage (ICH), additional CT scan was performed at the discretion of the investigators. Treatment with intravenous heparin, oral anticoagulants aspirin or volume expanders such as cystalloid and colloid or dextrans during first 24 hours after Alteplase administration was prohibited. General clinical condition such as neurological symptoms and cardiovascular status as well as pulmonary condition assessment were close observed every day in stroke until patients discharged. At discharge and 90-day follow up, the mRS range from 0 (no symptoms at all) to 6 (death), a score of 5 indicates severe disability (the patient is bedridden and incontinent and requires constant nursing care and attention) were assessed. Overall survival outcome and complications at 120-day were performed.

The primary end points were death, favorable outcome (a score of 0 or 1 on modified Rankin scale at discharge and 90-day) and ICH. The secondary end points were good outcomes (improvement of modified Rankin scale-mRS by final score 0-1 or improvement ≥4 points at discharge or 90-day, absent of ICH within 36 hours treatment, survived at 90-day and short hospital length of stay (LOS) <7 days), Improved mRS at discharged and 90-day, number of patients with length of hospital stay <7 days and overall complications.

In Cohort A, randomized controlled trial was performed. The patients were randomly assigned to receive intravenous 0.6 mg or 0.75 mg or 0.9 mg of

Alteplase per kilogram body weight in a 1:1:1. Interim analysis was performed; sample size re-calculation was performed to enroll more patient in Cohort B (Figure 1 and 2).

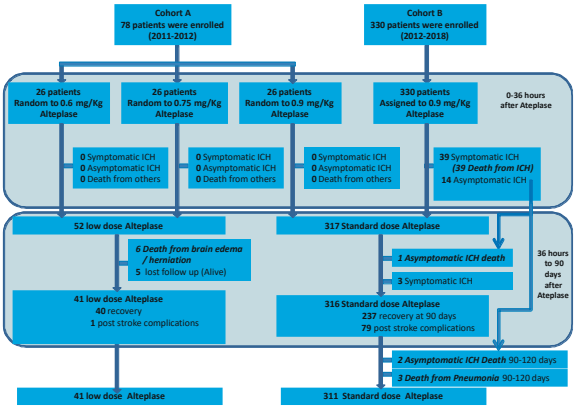

Figure 1: The number of patients who were enrolled to cohort A and B.

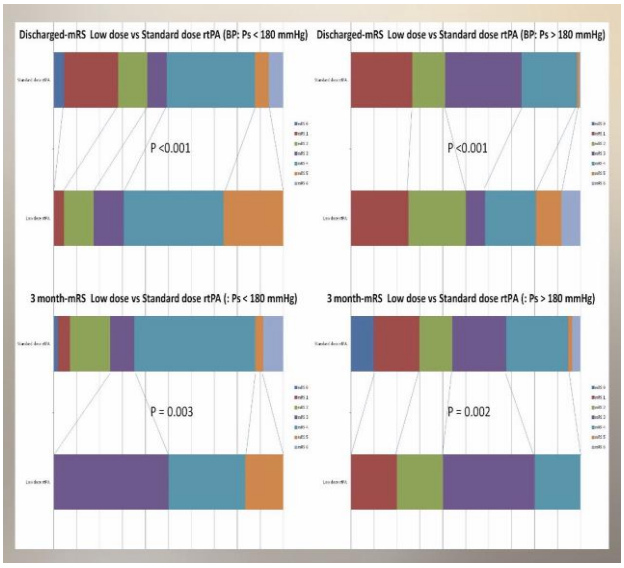

Figure 2: Distribution of Scores on the Modified Rankin Scale. distribution of scores is shown for the intention-to-treat population (at discharge and 90 days). In the intention-to-treat population, stratified analysis of the score distribution showed a significant difference between the study groups (P-0.02 for both comparisons by the Pearson chi-square test. The scores on the modified Rankin scale indicate the following: 0, no symptoms at all; 1, no significant dis- ability despite symptoms (able to carry out all usual duties and activities); score 2, slight disability (unable to carry out all previous activities help but able to walk without assistance); 4, moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs after own affairs without assistance); 3, moderate disability (requiring some without assistance); 5, severe disability (bedridden, incontinent and requiring constant nursing care and attention); 6, death . The population with initial systolic blood pressure <180 mmHg (left panel), standard-dose Alteplase showed significant better mRS of 0-1 and mRS of 0-3 at discharge (upper bars) and significant better mRS of 0-1 and mRS 0-2 at 90-day (lower bars) but more patients with mRS of 6 both discharge and 90-day. The population with initial systolic blood pressure >180 mmHg (Right panel), low-dose Alteplase showed significant better mRS of 0-2, at discharge (upper bars) and significant better mRS of 0-3 and mRS 5-6 at 90-day (lower bars) but more patients with mRS of 5-6 at discharge and 90-day.

5. Statistical Analysis

Descriptive statistical analysis (number, percent, mean, standard deviation, median) were used to describe the demographic data. Paired t-test was used to compare mean of ratio scale data. In the interim analysis, comparison the number of patients with favorable outcomes between 0.6 mg, 0.75 mg and 0.9 mg of Alteplase per kilogram body weight were analyzed by Person's Chi-square. Comparison the ratio of patients between low-dose and standard dose were analyzed by Fisher's Exact test. Relative risk with 95% confidence interval of each primary and secondary outcomes were calculated in both Per-Protocol (PP) and Intent-to Treat (ITT) population. To identify the factor predicting of death, intra-cerebral hemorrhage, good stroke outcomes, improved in mRS and short length of hospital stay <7 days were analyzed by Fisher's Exact and multinomial logistic regression.

6. Results

Between October 1, 2011 and September 30, 2012, a total of 78 patients were randomly assigned to 3 treatment groups. Each 26 patients were assigned to receive 0.6 mg, 0.75 mg and 0.9 mg of Alteplase per kilogram body weight, after sign consent form. There were 0, 6, and 10 patients and 4, 6, and 10 patients in 0.6 mg, 0.75 mg and 0.9 mg of Alteplase per kilogram body weight had favorable outcome at discharge and 90-day, respectively (0.0% *vs.* 23.0% *vs.* 38.4%; P=0.0004 at discharge and 15.3% *vs.* 23.0% *vs.* 38.4%; P=0.05 at 90-day). All patients in cohort A had no ICH. Although the statistical power <0.8, we stop enrolled low-dose Alteplase group, since standard-dose Alteplase had better efficacy, By using alpha error of 0.025 and beta error of 0.2, estimated probability of favorable outcome in standard-dose

Alteplase by 0.38 and estimated probability of favorable outcome in low-dose of Alteplase per kilogram body weight by 0.19. The sample size of standard-dose Alteplase was re-calculated to be 334, to achieve alpha error 0.025 and power of 0.8.

Between October 1, 2012 and March 31, 2018, we enrolled 330 patients into standard-dose Alteplase. Finally, total of 408 patients were enrolled. Each 26, 26 and 356 patients were assigned to receive 0.6 mg, 0.75 mg and 0.9 mg of Alteplase per kilogram body weight, respectively. Baseline demographic and clinical characteristics of the low-dose and standard-dose were showed in Table 2.

Table 2: Demographic and Baseline Characteristic of all patients, Low-dose Alteplase Group, Standard dose Alteplase Group and P Value between Low-dose Alteplase Group, Standard dose Alteplase Group and P Value.

Characteristic	All patients	Low-dose Alteplase	Standard dose Alteplase	P Value*
Number (percent)	408 (100)	52 (12.75)	356 (87.25)	-
Age (year)	56.1 (16.8)	55.0 (15.9)	56.3 (16.3)	0.59
Gender N (percent)				
Male	180 (44.12)	29 (55.78)	151 (42.42)	0.07
Female	228 (55.88)	23 (44.23)	205 (57.58)	-
Weight (Kg) mean (sd)	55.2 (27.3)	59.2 (22.4)	53.8 (24.9)	0.14
NIHSS (baseline)				
6-10	198 (48.50)	20 (38.44)	178 (50.00)	-
11-15	144 (27.94)	19 (36.54)	95 (26.69)	-
16-20	57 (13.97)	13 (25.00)	44 (12.36)	0.004
20-25	37 (9.06)	0 (0.00)	37 (10.39)	-
>25	2 (0.49)	0 (0.00)	2 (0.56)	-
Median NIHSS (IQR)	15 (10-20)	12 (10-15)	15 (10-20)	-
Stroke subtype				
Large infarction	138 (33.82)	21 (40.38)	118 (33.14)	-
Cardioembolic	100 (24.50)	11 (21.15)	89 (25.00)	-
Lacunar infarction	137 (33.57)	12 (23.07)	125 (35.11)	0.09
Other	1 (0.24)	0 (0.00)	1 (0.28)	-
Undetermined	31 (7.59)	8 (15.38)	23 (6.46)	-
Initial Systolic pressure (mmHg)				
<140	1 (0.25)	0 (0.00)	1 (0.28)	-
140-180	288 (70.58)	16 (30.76)	272 (76.40)	<0.001
≥180 - <200	79 (19.36)	19 (36.53)	60 (18.85)	-
≥200	40 (9.80)	17 (32.69)	23 (6.46)	-
Hypertension	209 (51.23)	25 (48.07)	184 (51.68)	0.65
Dyslipidemia	123 (30.15)	9 (17.31)	114 (32.02)	0.03
Atrial fibrillation	83 (20.34)	11 (21.15)	72 (20.22)	0.85
Diabetes mellitus	64 (15.69)	9 (17.31)	55 (13.76)	0.67
Current smoker	61 (14.95)	12 (23.07)	49 (13.76)	0.09

Coronary heart disease	37 (9.07)	6 (11.53)	31 (8.70)	0.44
Prior stroke	27 (6.62)	3 (5.76)	24 (6.74)	1
Prior cancer	10 (2.45)	1 (1.92)	9 (2.52)	1
Onset to needle Median Mean (sd)	2 hours 49 minutes 144.5 (48.1)	2 hours 16 minutes 137.9 (39.1)	2 hours 19 minutes 145.4 (49.3)	0.85**

*P Value was obtained by the Fisher's Exact test.

**P Value was obtained by paired t-test.

The initial NIHSS was significant higher stroke severity (NIHSS≥16) and dyslipidemia in standard-dose group.

The initial blood pressure was significant higher in low-dose especially in patients with initial systolic blood pressure >180 mmHg. Other baseline characteristics were not significant different between low-dose and standard-dose Alteplase. The median time of Alteplase administration by 2 hours 49 min. There were no different of onset to needle between low-dose and standard-dose Alteplase (137.9±39.1 minute *versus* 145.4±49.3-minute, P=0.85).

Primary end points

There were no different of death at 90-day and 120-day between low-dose and standard-dose Alteplase (11.5% *vs.* 11.2%, per-protocol relative risk 1.13 [95% CI 0.50-2.53; P=0.75], intent-to-treat relative risk 1.02 [95% CI 0.45-2.30; P=0.94] at 90-day and 11.5% and 12.6% per-protocol relative risk 1.00 [95% CI 0.45-2.23; P=0.98], intent-to-treat relative risk 0.91 [95% CI 0.40-2.03; P=0.82] at 120-day. Both discharge and 90-day mRS 0-1 in standard dose Alteplase were significantly higher in standard dose Alteplase group (40.1% *vs.* 3.8%; per-protocol relative risk 1.17 [95% CI 1.08-1.27; P<0.001], intent-to-treat relative risk 1.18 [95% CI 1.09-1.27; P<0.001] and 40.1% *vs.* 19.2%; per-protocol relative risk 1.26 [95% CI 1.03-1.53; P=0.01], intent-to-treat relative risk 1.255 [95% CI 1.07-1.46 ; P=0.003], respectively) (Table 3).

Table 3: Number (percent) of patients, Per-protocol odds ratio and Intent-to-treat odd ratio, Per-protocol Relative risk and Intent to treat Relative risk, for Primary End Points and Secondary End Points1.

End Point	Low-dose Alteplase	Standard dose Alteplase	P Value*	PP Relative risk (95% CI)	P Value	ITT Relative risk (95% CI)	P Value
Primary end points							
Death (90-day)	6 (11.5)	40 (11.2)	0.82	1.13 (0.50-2.53)	0.75	1.02 (0.45-2.30)	0.94
Death (120-day)	6 (11.5)	45 (12.6)	0.88	1.00 (0.45-2.23)	0.98	0.91 (0.40-2.03)	0.82
mRS score of 0-1 at discharge***	2 (3.8)	66 (40.1)	0.007**	1.17 (1.08-1.27)	<0.001	1.18 (1.09-1.27)	<0.001
mRS score of 0-1 at 90-day***	10 (19.2)	127 (40.1)	0.019**	1.26 (1.03-1.53)	0.01	1.25 (1.07-1.46)	0.003
Intra-cerebral hemorrhage (ICH) in first 36 hours	0 (0.0)	53 (14.8)	0.0005	0.06 (0.00-1.00)	0.05	0.06 (0.00-1.00)	0.05
Intra-cerebral	0 (0.0)	56 (15.7)	0.0003	0.06 (0.00-	0.05	0.05 (0.00-	0.04

hemorrhage (ICH) total				1.10)		0.95)	
Symptomatic ICH in first 36 hours	0 (0.0)	39 (10.9)	0.004	0.09 (0.00-1.50)	0.09	0.08 (0.00-1.36)	0.08
Symptomatic ICH Total	0 (0.0)	42 (11.7)	0.002	0.08 (0.05-1.39)	0.08	0.07 (0.00-1.26)	0.07
Asymptomatic ICH*	0 (0.0)	14 (3.9)	0.15	0.22 (0.01-3.71)	0. 29	0.20 (0.01-3.38)	0.26
Secondary end points							
Good out comes at discharged****	35 (67.3)	204 (57.3)	0.08	0.76 (0.50-1.15)	0.19	0.76 (0.50-1.15)	0.19
Improved mRS at discharged***	17 (32.6)	152 (42.6)	0.17	1.17 (0.95-1.44)	0.13	1.17 (0.95-1.44)	0.13
initial BP ≤180	14 (30.4)	132 (44.1)	0.08	1.24 (1.00-1.54)	0.04	1.24 (1.00-1.54)	0.04
initial BP >180	3 (50.0)	20 (35.0)	0.42	0.77 (0.33-1.75)	0.53	0.77 (0.33-1.753)	0.53
Improved mRS at 90-day***	25 (48.0)	245 (68.8)	0.003	1.61 (1.05-2.48)	0.02	1.66 (1.22-2.25)	0.001
initial BP ≤180	21 (45.6)	212 (70.9)	0.0009	2.05 (1.30-3.23)	0.001	1.86 (1.35-2.56)	0.0001
initial BP >180	4 (66.66)	33 (57.8)	0.66	0.47 (0.08-2.81)	0.41	0.79 (0.24-2.55)	0.69
Length of hospital stay <7 days	36 (69.2)	280 (78.8)	0.12	1.69 (0.89-3.20)	0.1	1.44 (0.91-2.26)	0.11
Complications 4 month	7 (13.4)	79 (22.1)	0.15	0.60 (0.29-1.24)	0.17	0.60 (0.29-1.24)	0.17

*P Value was obtained by the Fisher's Exact test

**P Value was obtained by the Pearson chi-square test of proportion

***Score on the modified Rankin scale (mRS) range from 0 (no symptom at all) to 6 (death)

****Good outcomes defined as improvement of modified Rankin scale-mRS by final score 0-1 or improvement ≥ 4 points at discharge or 90-day, absent of intracranial hemorrhage within 36 hours treatment, survived at 90-day and short hospital length of stay (LOS) < 7 days)

PP- Per Protocol, ITT- Intent-To-Treat.

There were no ICH in low dose Alteplase group (0.0%) *vs.*14.8 % in standard dose Alteplase (per-protocol and intent-to-treat relative risk 0.06 [95% CI 0.00-1.00; P=0.05] at 36 hours and 0.0% *vs.* 15.7% per-protocol relative risk 0.06 [95% CI 0.00-1.10; P=P=0.05], intent-to-treat relative risk 0.05 [95% CI 0.00-0.95; P=0.04] at 120-day. There were no symptomatic ICH in low-dose Alteplase group 0.0% *vs.*10.9 % in standard-dose Alteplase (per-protocol relative risk 0.09 [95% CI 0.00-1.50; P=0.08], intent-to-treat relative risk 0.09 [95% CI 0.00-1.36; P= 0.08] at 36 hours) and 0.0% *vs.* 11.79% (per-protocol relative risk 0.08 [95% CI 0.05-1.39; P=0.08]; intent-to-treat relative risk 0.07 [95% CI 0.00-1.26; P=0.07] at 120-day. There were no different of asymptomatic ICH at 36 hours and 120-day between low-dose and standard-dose Alteplase 0.0% *vs.* 3.93% (per-protocol relative risk 0.22 [95% CI 0.01-3.73; P=0.29], intent-

to-treat relative risk 0.20 [95% CI 0.01-3.38; P=0.26] at 36 hours and 120-days (Table 3).

Secondary end points

There were no different of number of patients with good outcomes at discharge between low-dose and standard-dose Alteplase (67.3% *vs.* 57.3%, per-protocol and intent-to-treat relative risk 0.76 [95% CI 0.50-1.15; P=0.19]. Interestingly, there were significantly higher number of patient with improved mRS in standard-dose Alteplase who had initial systolic blood pressure less than 180 mmHg at discharge and 90-day (44.1% *vs.* 30.4%; per-protocol and intent-to-treat relative risk 1.24 [95% CI 1.00-1.54; P=0.04] and 70.9% *vs.* 45.6%, per-protocol relative risk 2.05 [95% CI 1.30-3.23; P=0.001], intent-to-treat relative risk 1.86 [95% CI 1.35-2.56; P=0.0001].

However; there were no significantly different in number of patient with improved mRS in low-dose compare to standard-dose Alteplase who had initial systolic blood pressure >180 mmHg at discharge and 90-days (50.0% *vs.* 35.0%, per-protocol and intent-to-treat relative risk 0.77 [95% CI 0.33-1.75; P=0.53] and 66.6% *vs.* 57.8%, per-protocol relative risk 0.47 [95% CI 0.08-2.81; P=0.41]; intent-to-treat relative risk 0.79 [95% CI 0.24-2.55; P=0.69] (Table 3).

Interestingly, the patients with initial systolic blood pressure >180 mmHg, more patients with mRS 0-3 at 90-day with low-dose than standard-dose Alteplase (P=0.002) and less patients with 90-day of mRS 4-6 with low-dose than standard-dose Alteplase (P=0.002). There were no different of number of patient with short LOS <7 days between low-dose and standard-dose Alteplase (69.2% *vs.* 78.8% per-protocol relative risk 1.69 [95% CI 0.89-3.27; P=0.10], intent-to-treat relative risk 1.44 [95% CI 0.91-2.26; P=0.11]. Overall complications were not significant different between standard dose compared to low-dose Alteplase group 13.4% *vs.*22.1%. per-protocol and intent-to-treat relative risk 0.60 (0.29-1.24) (P=0.15).

Factors predicting good outcome composed of no atrial fibrillation, lacunar infarction and better initial NIHSS (p<0.02). Factors predicting improved mRS at discharge composed of initial lacunar infarction and better initial NIHSS. Factors predicting death composed of onset to needle time >180 min, initial large infarction, large embolic stroke and worse initial NIHSS (p<0.04). Factors predicting ICH composed of large infarction, large embolic stroke and worse initial NIHSS (p<0.002). Factors predicting prolonged hospital length of stay more than 7 days were atrial fibrillation initial large infarction, cardio-embolic stroke and worse initial NIHSS (p <0.001).

Safety

A total of 51 patients died, 6 of the 52 patients in low-dose alteplase die from brain herniation although wild craniectomy were performed and 45 of the 356 in the standard dose alteplase. Of these 39 died between 0-36 hours, 3 died between 36 hours-90-day. There was 1 asymptomatic ICH death from severe pneumonia after 36 hours and 3 patients with new symptomatic ICH after 36 hours after treatment. Moreover, in standard-dose alteplase group, 2 asymptomatic ICH patients and 3 non-ICH patients die from pneumonia after prolonged hospitalization more than 90-day admission. There were 79 (22.4%) patients with post stroke complications in the standard dose Alteplase when compared to 7 (13.45) patient in low-dose Alteplase (P=0.15). The details of complication showed in Table 4.

Table 4: Complications of all patients, Low-dose Alteplase Group, Standard dose Alteplase Group and P Value.

Complication N (%)	Low-dose Alteplase	Standard-dose Alteplase	P Value*
Intra-cerebral hemorrhage	0 (0.0)	56 (15.7)	0.003
Symptomatic	0 (0.0)	42 (11.7)	0.002

Asymptomatic	0 (0.0)	14 (3.9)	0.2
Symptomatic brain edema	6 (11.5)	28 (7.8)	0.31
Post stroke seizure	0 (0.0)	2 (0.5)	0.64
Pneumonia	3 (5.7)	4 (1.1)	0.02
Acute Myocardial infarction	1 (1.9)	6 (1.6)	0.59
Urinary tract infection	0 (0.0)	2 (0.5)	0.64
Electrolyte abnormality	2 (3.8)	3 (0.8)	0.07
Total number of patients	7 (13.4)	79 (22.1)	0.15
Total events	10	101	0.17
Death (in 120 days)	6 (11.5)	45 (12.6)	0.88
Symptomatic brain edema without hemorrhage	5 (11.5)	0 (0.0)	<0.001
Symptomatic brain edema with acute myocardial infarction	1 (1.9)	0 (0.0)	0.03
Intra-cerebral hemorrhage	0 (0.0)	42 (11.7)	0.002
Symptomatic	0 (0.0)	39 (10.9)	0.004
Asymptomatic with secondary brain edema	0 (0.0)	3 (0.8)	0.76
Pneumonia	0 (0.0)	3 (0.8)	0.76

*P Value was obtained by the Fisher's Exact test.

7. Discussion

Interim analysis of cohort A, randomized control trial; demonstrated inferior efficacy of low-dose Alteplase to standard dose in favorable outcome (P=0.004 at discharge and P=0.05 at 90-day) without adequate power of 0.8. Since the interim analysis demonstrated less patients had favorable outcome in 0.6 mg and 0.75 mg of Alteplase per kilogram body weight (low-dose) than standard-dose, data monitoring advisory board of National Health Organization of Thailand recommend to stop enrollment of low-dose Alteplase. The statistical analysis was re-calculated the sample sized by using preliminary data of favorable outcome in Cohort A. By using alpha error of 0.025 and beta error of 0.2, estimated probability of favorable outcome in standard-dose Alteplase by 0.38 and estimated probability of favorable outcome in low-dose of Alteplase by 0.19. Interestingly, after enrolled more 330 patients into standard dose Alteplase, the different efficacy of favorable outcomes in low-dose Alteplase can be demonstrated with adequate power of 0.8.

This study design enrolled all moderate to stroke severity (NIHSS≥6, if the patients had onset to needle less than 3 hours and NIHSS of 6-26 if the patients had onset to needle of 3 hours to 4.5 hours). When compared to ECASS study which exclude the severe stroke case from the trial, this study enrolled maximum NIHSS of 25 and the maximum onset to needle is 4.5 hours, as same as the ECASS and ENCHANTED study [3-5,7]. The initial severity, NIHSS, is the most strong predictor of functional and neurological outcomes. In this study, the standard-dose Alteplase had more severe patients (NIHSS≥16), but had more favorable outcome at discharge and 90-day. These findings confirmed the superior efficacy of standard-dose over low-dose Alteplase, especially in the patients with initial systolic blood pressure <180 mmHg. There were no significant different of baseline characteristic of age, gender, weight, stroke subtypes, hypertension, atrial fibrillation, diabetes mellitus, current smoker, coronary heart disease, prior stroke and prior cancer between low-dose and standard-dose Alteplase. Only initial systolic pressure >180 mmHg significantly higher in low-dose Altepalse. However, all patients were treated until

systolic pressure <180 mmHg in all cases, before administration of low-dose and standard-dose Alteplase.

The previous major stroke studies reported the successful acute stroke treatment with 0.9 mg of Alteplase per kilogram body weight within 3 hours to 4.5 hours after stroke onset [1-6]. However; bleeding complications especially symptomatic and asymptomatic ICH were major concerned. Compared to ENCHANTED trial [7], which showed no clear differential benefits of low dose Alteplase in disability outcomes, in the aspect of age, race and ethnicity and neurological severity, this study first established significant reduction of total ICH and in low-dose Alteplase, without significant different of stroke death. Interestingly the blood pressure arm of ENCHANTED trial part B [13] is scheduled to be complete in 2018, Authors reported no significant interactions between intensity of blood pressure lowering and Alteplase dosing on the risk of major symptomatic hemorrhage. This study first established benefits of low-dose Ateplase in significant reduction of moderately severe to severe disability and death (mRS 4-6) at 90-day and better rate of mRS 0-3 at 90-day, in patients with initial high systolic blood pressure >180 mmHg Since low dose, 0.6 mg/kg Alteplase was approved for standard guideline in Japan, Pakistan and Vietnam in patients with all ranged initial systolic blood pressure and in large thromboembolic stroke subtype within 3 hours after stroke onset.

This study confirmed inferiority of low-dose Alteplase in the patients with initial systolic blood pressure <180 mmHg, since more patient's recovery with favorable outcomes at discharge and 90-day in standard dose than low-dose Alteplase. Although significant higher ICH in standard dose group was observed, overall complications and death rate were not different.

Early treatment remains essential factor for re-canalization of cerebral blood vessels. When compared to Japan Alteplase Clinical Trial (J-ACT) [14] which had 100.0% Asians, prospective, single-arm, open label trial of 0.6 mg of Alteplase per kilogram body weight within 3 hours, mean onset-to-needle time 151.0 minutes and median NIHSS of 15, (IQR 5-30), in low-dose Alteplase, in mainly cardioembolic stroke (80%) and atherothrombotic (11.7%), reported the favorable outcome of 36.9% and symptomatic ICH of 5.8% in 103 patients at 3-month and when compared to SAMURAI registered data base [15] which had 100.0% Asians, prospective, single-arm, open label trial of 0.6 mg of Alteplase per kilogram body weight within 3 hours, mean onset-to-needle time 145.0 minutes and median NIHSS of 13, (IQR 7.3-19), in low-dose Alteplase, in mainly cardioembolic stroke (63.3%) and atherothrombotic (15.2%), reported the favorable outcome of 33.2% and symptomatic ICH 3.8% in 600 patients at 3-month, in this study which had 100.0% Asians, with onset to needle within 4.5 hours, mean onset-to-needle time of 137.9 minute and median NIHSS of 12 (IQR 10-15), which less than J-ACT and SAMURAI registered data base in low-dose Alteplase, had less favorable outcome of 19.2%, at 90-day and symptomatic ICH of 0.0% in 52 patients at 90-day [14,15].

This different may be effected by majority of large thromboembolic stroke subtype in this study when compared to mainly cardio-embolic stroke subtype in J-ACT and SAMURAI registered data base. These finding showed the impact of stroke subtype on favorable outcome, especially in cardio- embolic stroke as the good candidate. Moreover, longer onset-to-needle time may increased risk of symptomatic hemorrhage (Table 5).

When compared to ENCHANTED study [7], which had 63.2% Asians, median onset-to-needle time 170 minutes and median NIHSS of 8 (IQR 5-14) in low-dose Alteplase, in mainly large artery occlusion (38.3%) and cardioembolic stroke (19.9%), with favorable outcome of 46.8% and symptomatic ICH of

1.0% by SITS-MOST criteria and 5.9% by NINDS criteria in 1654 patients at 36 hours. This study with 100.0% Asians, median onset-to-needle time of 136 minutes and median NIHSS of 12 (IQR 10-15), in low-dose Alteplase, in mainly large artery occlusion (40.3%) and cardio-embolic stroke (21.1%), had less favorable outcome of 19.2%, at 90-day and symptomatic ICH of 0.0%. These finding showed the impact of baseline NIHSS on favorable outcome, especially in lower NIHSS as the good candidate. Moreover, shorter onset-to-needle time may not increase favorable outcome, but may reduce risk of symptomatic hemorrhage in low-dose Alteplase (Table 5).

Table 5: Comparison of Japanese Alteplase Clinical Trial, Enhanced Control of Hypertension and Thrombolysis Stroke (ENCHANTED) study and This study in Low-dose Alteplase and overall Population in the aspect of main subtype of stroke, initial severity (NIHSS), onset to needle time, percent of Asian participant, Favorite outcome, Symptomatic Intra-cerebral Hemorrhage and Death in 3 month/90-day.

Low-dose Alteplase study	Number (N)	Cardioembolic stroke N (%)	Largre cerebral infarction/ Artherosclerosis N (%)	Median NIHSS (Inter Quartile Range)	Mean Onset to neddle time (minute)	Asian patient enrolled (%)	Favorite outcome percent (95% CI)	Symptomatic Intra-cerebral Hemorrhage percent (95%CI)	Death in 3month/ 90-day percent (95%CI)
J-ACT	103	83 (80.0)	11 (11.1)	15 (5-30)	151	100	36.9 (27.5-46.9)	5.8 (2.1-12.2)	9.7 (4.7-17.1)
SAMURAI	600	380 (63.3)	91 (15.2)	13 (7.3-19)	145	100	33.2 (29.5-37.0)	3.8 (2.6-5.7)	7.2 (5.4-9.5)
ENCHANTED	1607	320 (19.9)	616 (38.3)	8 (5-14)	170	63.2	48.1 (45.7-50.6)	5.9 (4.8-7.1)	8.7 (7.3-10.2)
This study	52	11 (21.1)	21 (40.3)	12 (6-25)	137.9	100	19.2 (9.6-32.5)	0.0 (0.0-6.8)	11.5 (4.3-23.4)
Overall study	2362	423 (33.9)	655 (31.5)	NA	162.1	74.9	43.2 (41.2-45.2)	5.2 (4.9-6.9)	5.2 (4.3-6.1)

In this study, all patients transferred from the rural area around the hospital were referred to the emergency room by "Thai referral network corroboration" effectively with better onset-to-needle time when compared to J-ACT, SAMURAI and ENCHANTED study [7,14,15]. So, the onset-to-needle time may be key factor determine ICH in low-dose Alteplase administration.

The previous study in Thailand reported the factors predicting risk of ICH and death [9-12].

Most of study show high blood pressure and worse NIHSS>15, old age, hyperglycemia, ASPECT score <8 for asymptomatic ICH and ASPECT score for symptomatic ICH and abnormal CT scan "dense in

MCA sign" or large DWI volume in MRI, large infarction and large embolic stroke associated with increased risk of hemorrhage [9-12]. When compare to previous studies, severe NIHSS, high glucose increased risk of death, in this study, longer onset to needle time, large embolic stroke, NIHSS>16, large infarction, atrial fibrillation and smoking also increased risk of stroke death. For poor stroke outcomes, previous study showed aging and female increased risk of poor outcomes. This study showed poor stroke outcome in patient with atrial fibrillation, high NIHSS>16 and large infarction, large embolic stroke associated with poor stroke outcomes. The factors predicting-improved mRS after Alteplase included low NIHSS and small infarction, non-large embolic stroke as well as factors predicting prolonged hospital stay >7 days including atrial fibrillation, high NIHSS and large infarction and large embolic stroke.

8. Conclusion

In conclusion, as compared with standard-dose, intravenous low-dose Alteplase administered within 4.5 hours after the onset of stroke significant less favorable outcome, intra-cerebral hemorrhage and complications, but not different in death and length of hospital stay in the patients with initial systolic blood pressure <180 mmHg. However, patients with initial systolic blood pressure >180 mmHg, intravenous low-dose Alteplase had less disability at 90 day and more patients with mRS 0-3 at discharged and 90-day with decreased risk of intra-cerebral hemorrhage. Further double-blinded randomized control trial compares the efficacy of Low dose and standard dose Alteplase in the patients with initial systolic blood pressure >180 mmHg after treated with intravenous nicardipine to control systolic blood pressure <180 mmHg before Alteplase administration should be performed.

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