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Safety and Efficacy Comparison of Tenecteplase and Alteplase for Clinically Suspected Large Vessel Occlusion Strokes without Thrombectomy

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Tenecteplase · Tissue plasminogen activator · Thrombolysis · Ischaemic stroke

Abstract

Introduction: Tenecteplase is a thrombolytic with higher fibrin affinity and is potentially better in clot lysis. A higher spontaneous recanalisation rate for large vessel occlusion (LVO) strokes had been shown in comparison studies with alteplase. Results of the LVO studies reflect the composite effect of the thrombolytic and thrombectomy, as patients would be treated by thrombectomy had they not been recanalised by intravenous thrombolysis alone. Thrombectomy is not readily available in many parts of the world. Our study aimed to compare the outcomes of suspected LVO patients treated with tenecteplase versus alteplase only, without the confounding effect of thrombectomy. ***Methods:*** This is a retrospective review. Data of patients given tenecteplase from May 2020 to August 2023 and those given alteplase 0.9 mg/kg from January 2019 to August 2023 were retrieved. Due to fluctuation in supply of tenecteplase during the COVID pandemic, some LVO patients were given alteplase. Patients with anterior circulation, clinically suspected LVO strokes (defined as National Institutes of Health Stroke Scale (NIHSS) score ≥6, plus cortical signs or hyperdense vessel sign), with thrombolysis given within 4.5 h of stroke onset were analysed. Patients with thrombectomy done were excluded. Safety and efficacy outcomes were compared. ***Results:*** There were 245 tenecteplase-treated patients treated between May 1, 2020, and August 31, 2023, and 732 patients were treated with alteplase between January 1, 2019, to August 31, 2023. Out of these, 148 tenecteplase patients and 138 alteplase 0.9 mg/kg patients fulfilled the study criteria. The symptomatic intracerebral haemorrhage rate was non-significantly lower in the tenecteplase group (2.1% vs. 5.8%, $p = 0.13$). There were no significant differences in the rate of ≥8-point NIHSS improvement (23.6% vs. 23.7%, $p = 1$) or the ≥4-point improvement (40.5% vs. 40.7%, $p = 1$) at 24 h. At 3 months, 21.6% of tenecteplase patients had good functional outcome (modified Rankin scale [mRS] 0–2), compared to 26.3% in the alteplase group ($p = 0.40$). ***Conclusion:*** In this pragmatic study of clinically suspected anterior circulation LVO patients without thrombectomy, outcome solely reflects the effects of tenecteplase. Tenecteplase showed comparable

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safety and efficacy to alteplase, but the result should be interpreted with caution in view of its small sample size and non-randomised study design.

Introduction

Approximately 20–30% of all strokes are due to large vessel occlusions (LVOs) [1, 2]. The recanalisation rate by intravenous alteplase is low for LVO strokes with higher clot burden [3]. Tenecteplase has higher fibrin affinity, greater resistance to inactivation by plasminogen activator inhibitor, potentially translating into higher efficacy in clot lysis and lower haemorrhagic complications. It has a longer half-life and can be administered as a single intravenous bolus, this being an advantage over the 1-h infusion that alteplase needs [4].

The Extend-IA TNK trial showed a significantly higher proportion of LVO patients achieving recanalisation already by intravenous tenecteplase alone prior to planned thrombectomy when compared to alteplase. There was no increase in intracerebral haemorrhage (ICH), and the functional outcome was more favourable [5]. Subsequently, the large randomised controlled AcT trial of tenecteplase for all thrombolysis-eligible patients was performed. It showed tenecteplase was non-inferior to alteplase [6]. For patients in the EXTEND-IA TNK and AcT trials, patients with LVOs would have mechanical thrombectomy proceeded if the intravenous thrombolytic had not successfully recanalised the vessel [5, 6]. So the safety and efficacy outcomes actually reflected the composite effect of the intravenous thrombolytic and mechanical thrombectomy.

Our study aimed to compare only the effect of tenecteplase with alteplase, without the confounding effect of thrombectomy. In particular, we aimed to study LVOs because patients with LVO are the ones which would have more severe strokes, larger infarcts, and higher risk of haemorrhagic transformation if the vessel is not recanalised. And if tenecteplase does have a higher rate of recanalisation than alteplase, these LVO patients are the ones with the most to gain. This is important as mechanical thrombectomy may not be readily available in all parts of the world.

There are limited data on this specific group of patients without thrombectomy, as many published papers are from centres with mechanical thrombectomy provision. In the study by Qureshi et al. [7], patients from thrombectomy and non-thrombectomy centres were included to compare the outcomes of tenecteplase and alteplase. A higher rate of any intracranial haemorrhage in non-thrombectomy tenecteplase patients was found, but the rate of symptomatic intracranial haemorrhage was not reported. In their study, cortical signs were present in only about one-quarter of non-thrombectomy patients. Furthermore, the retrieval of information on any cortical signs was based on the International Classification of Diseases (ICD) coding, so these might be the presenting symptoms upon admission or as a consequence of thrombolytic complication. So, the non-thrombectomy patients in their study might have been LVOs or lacunar strokes as well. The CERTAIN collaboration study reported tenecteplase to be significantly associated with less symptomatic intracranial haemorrhages in both thrombectomy and non-thrombectomy patients [8]. It did not report whether the non-thrombectomy group patients were those with lacunar stroke presentation, or whether they were LVO patients but without thrombectomy due to no service provision.

Our hospital started use of tenecteplase 0.25 mg/kg for LVOs (angiographically proven or clinically suspected) since May 2020, before it was well proven to be non-inferior for all thrombolysis-eligible patients in the later randomised trials. Our hospital did not have 24-h urgent computed tomography angiography (CTA) and endovascular service for acute ischaemic stroke patients during the time of our study. In the absence of CTA, as guidance to select which were the patients more likely to have LVOs and therefore to receive tenecteplase, we devised the "clinically suspected LVO" criteria. Presence of cortical signs and a higher National Institutes of Health Stroke Scale (NIHSS) score are predictors of having LVOs [9–11]. We used an NIHSS score ≥6 points, plus cortical signs or hyperdense vessel sign on plain CT brain as the clinical criteria to give tenecteplase for those patients without CTA. Whether tenecteplase is used instead of alteplase is at the discretion of the treating neurologist, and affected by supply fluctuations of tenecteplase related to the COVID pandemic. The brand of tenecteplase used was Metalyse (Boehringer Ingelheim), as off-label treatment for stroke.

Due to scarce information specifically on the effects of tenecteplase alone for LVOs without thrombectomy, we decided to perform this study to look into the data for our patients using the "clinical suspected LVO" criteria, focusing on anterior circulation LVO strokes in our hospital. Our study is a pragmatic study, aiming to review the safety and efficacy outcomes of tenecteplase versus alteplase (standard dose) for these suspected anterior circulation LVO strokes without thrombectomy. Such scenario has not been uncommon locally when provision of mechanical thrombectomy is only available in office hours in some hospitals.

Methods

This study is a retrospective comparison study of patients who received tenecteplase (0.25 mg/kg) versus standard dose alteplase (0.9 mg/kg) within the 4.5-h time window in our hospital. Data of tenecteplase patients treated from May 2020 to August 2023 and alteplase patients treated from Jan 2019 to August 2023 were retrieved from our stroke thrombolysis registry and from the electronic patient record system. The "clinically suspected LVO" criteria used in our clinical practice for patients without CTA were used to select patients from our registry to be included in this study. That is, NIHSS score ≥6 points, plus cortical signs or have hyperdense vessel sign on plain CT brain. Excluded from this study were patients given thrombolytics beyond the 4.5-h time window, low-dose alteplase, thrombectomy patients, posterior circulation strokes, and stroke mimics. Only anterior circulation strokes were included to facilitate comparison of the baseline CT brain of the two groups using the Alberta Stroke Program Early CT Score (ASPECTS). Patients had CT brain done prior to thrombolysis and at 24 h after thrombolysis or if they have neurological deterioration.

Demographics, vascular risk factors, baseline NIHSS, ASPECTS, and treatment time parameters (symptom onset-to-needle time, door-to-needle time) were retrieved. Safety outcomes were the symptomatic ICH rate (based on the SITS-MOST criteria) [12], parenchymal haematoma type 2 rate, and 30-day all-cause mortality. Efficacy outcomes were an excellent (≥8 points) NIHSS improvement at 24-h post-thrombolysis or reaching 0–1, a good (≥4 points) NIHSS improvement at 24-h post-thrombolysis or reaching 0–1, and a good functional outcome of 0–2 on the modified Rankin scale (mRS) at 3 months.

Statistical analyses were conducted using the SPSS (IBM SPSS Statistics for Windows, Version 29.0.2.0 (20) Armonk, NY: IBM Corp). Categorical variables were compared with the Fisher's exact test. Comparison between medians of continuous variables was performed using the Mann-Witney U test. p values <0.05 were considered statistically significant. Missing data were not included in the outcome analysis.

Results

From May 1, 2020, till August 31, 2023, there were 245 tenecteplase-treated patients. 148 tenecteplase patients fulfilled the study criteria of "clinically suspected" anterior circulation LVO strokes without thrombectomy. From January 1, 2019, to August 31, 2023, there were 732 patients were treated with alteplase. Out of these, 138 alteplase 0.9 mg/kg patients fulfilled the study criteria and were compared to the tenecteplase patients.

Baseline parameters were similar (Table 1). Both groups had a median NIHSS of 20 and an ASPECTS of 9 on the baseline CT brain. The door-to-needle time was shorter in the tenecteplase group (59 vs. 70 min, $p < 0.05$). The symptomatic ICH rate was non-significantly lower in the tenecteplase group (2.1% (3/146) versus 5.8% (8/137), $p = 0.13$). There were no significant differences in the rate of excellent outcome of ≥8-point NIHSS improvement or reaching 0–1 (23.6% (35/148) versus 23.7% (32/135), $p = 1$) or good outcome of ≥4-point improvement or reaching 0–1 (40.5% [60/148] versus 40.7% [55/135], $p = 1$) at 24 h. The 30-day mortality rate was similar.

At 3 months, there were 5 patients in the alteplase group which were lost to follow-up. 21.6% of tenecteplase patients had good functional outcome (mRS 0–2), compared to 26.3% (35/133 patients) in the alteplase group ($p = 0.40$) (Table 2).

In this study on non-thrombectomy patients, there were a few patients in this registry who fulfilled the "clinical suspected LVO" criteria without endovascular therapy but had CTA done which showed no LVO but had distal occlusions, no occlusion, and just stenosis. We did not exclude these patients. We aim to include all patients with the same clinical criteria, irrespective of whether CTA had been done with LVO excluded in this pragmatic study. As a result, the study result could be applicable to patients treated according to the clinical criteria, irrespective of any CTA performed and their findings.

In the alteplase group, 5 patients had CTA before thrombolysis – 3 had distal occlusions and 2 had no evident occlusion. In the tenecteplase group, 21 patients had CTA before thrombolysis – 8 had distal occlusions, 6 had no evident occlusion, the others had LVO but no endovascular therapy (2 spontaneous recanalisation on digital subtraction angiography, 1 refused endovascular therapy, 4 deemed by operator not suitable for operation). After we excluded all the 26 patients with CTA done, comparisons were performed only on patients who fulfilled the clinical criteria without CTA performed. It was then fully in line with the aim of this pragmatic study. There were no statistical differences in outcomes (Table 3).

Discussion

LVO strokes are known to have lower recanalisation rates by alteplase, but mechanical thrombectomy is not always available around the world. Tenecteplase has shown

Table 1. Baseline characteristics of tenecteplase and alteplase patients

	Tenecteplase, May 2020 to August 2023 (n = 148)	Alteplase, Jan 2019 to August 2023 (n = 138)	p value
Age, median (IQR), years	81 (IQR 18.5)	79 (IQR 19)	0.28
Male	65 (43.9%)	70 (50.7%)	0.29
History of stroke/TIA	30 (20.3%)	35 (25.4%)	0.33
Hypertension	110 (74.3%)	106 (76.8%)	0.68
Diabetes mellitus	37 (25%)	47 (34.1%)	0.12
Atrial fibrillation	82 (55.4%)	70 (50.7%)	0.48
Hyperlipidaemia	63 (42.6%)	51 (37.0%)	0.34
Ischaemic heart disease	24 (16.2%)	24 (17.4%)	0.87
Onset-to-needle time, median (IQR), min	143 (IQR 81)	150 (IQR 85)	0.14
Door-to-needle time, median (IQR), min[a]	59 (IQR 25)	70 (IQR 31.5)	0.002
Baseline NIHSS, median	20 (IQR 15)	20 (IQR 13)	0.40
ASPECTS, median	9	9	0.34

ASPECTS, Alberta Stroke Program Early Computed Tomography Score; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack. [a]Data not applicable for in-patient strokes for 12 tenecteplase and 14 alteplase patients.

Table 2. Outcome comparison of tenecteplase and alteplase patients

	Tenecteplase, May 2020 to August 2023 (n = 148)	Alteplase, Jan 2019 to August 2023 (n = 138)	p value
Asymptomatic ICH[a]	16.4% (24/146)	16.1% (22/137)	1
Symptomatic ICH[a]	2.1% (3/146)	5.8% (8/137)	0.13
PH-2[a]	4.1% (6/146)	7.3% (10/137)	0.31
30-day mortality	14.9% (22/148)	18.8% (26/138)	0.43
NIHSS ≥4-point improvement at 24 h, or = 0, 1[b]	40.5% (60/148)	40.7% (55/135)	1
NIHSS ≥8-point improvement at 24 h, or = 0–1[b]	23.6% (35/148)	23.7% (32/135)	1
mRS 0–1 at 3 months[c]	16.9% (25/148)	23.3% (31/133)	0.18
mRS 0–2 at 3 months[c]	21.6% (32/148)	26.3% (35/133)	0.40

ICH, intracranial haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH-2, parenchymal haematoma; PH-2, parenchymal haematoma type 2. [a]For symptomatic ICH and PH-2, 2 tenecteplase patients and 1 alteplase patient had missing data. [b]For 24-h NIHSS outcome, 3 alteplase patients had missing data. [c]For 3-month mRS outcome, 5 alteplase patients had missing data.

promise in the EXTEND-IA TNK trial of LVO strokes with higher rate of spontaneous recanalisation before thrombectomy [5]. Real world registries and randomised controlled trials showed tenecteplase being non-inferior to alteplase [6, 13]. However, in these studies, if the patients had not had recanalisation by intravenous thrombolysis, mechanical thrombectomy would be proceeded for patients with LVOs. So the reported outcome reflected the composite effect of thrombolysis and thrombectomy. For studies which had analysed non-thrombectomy patients, there were insufficient data to distinguish whether these were lacunar strokes or LVO strokes [8].

Table 3. Outcome comparison of tenecteplase and alteplase patients (excluding patients with CTA done)

	Tenecteplase, May 2020 to August 2023 (n = 127)	Alteplase, Jan 2019 to August 2023 (n = 133)	p value
Symptomatic ICH[a]	2.4% (3/125)	6.1% (8/132)	0.22
PH-2[a]	4.8% (6/125)	7.6% (10/132)	0.44
NIHSS ≥4-point improvement at 24 h, or = 0, 1[b]	36.2% (46/127)	40.8% (53/130)	0.52
NIHSS ≥8-point improvement at 24 h, or = 0–1[b]	21.2% (27/127)	23.1% (30/130)	0.77
mRS 0–1 at 3 months[c]	13.4% (17/127)	22.5% (29/129)	0.07
mRS 0–2 at 3 months[c]	17.3% (22/127)	25.6% (33/129)	0.13

ICH, intracranial haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH-2, parenchymal haematoma; PH-2, parenchymal haematoma type 2. [a]For symptomatic ICH and PH-2, 2 tenecteplase patients and 1 alteplase patient had missing data. [b]For 24-h NIHSS outcome, 3 alteplase patients had missing data. [c]For 3-month mRS outcome, 4 alteplase patients had missing data.

In our study specifically studying patients with clinically LVOs without thrombectomy, the symptomatic ICH rate was similar between tenecteplase and alteplase. In vitro studies showed that, in contrast to alteplase adversely affecting the fibrinolytic system (decrease in fibrinogen levels, increased prothrombin time, increased inhibitor activity, and decreased plasminogen) potentially increasing the risk of bleeding, tenecteplase did not affect these parameters much [14]. Our study included patients who failed recanalisation with intravenous thrombolysis and had no rescue thrombectomy available. There was no suggestion of increased risk of reperfusion haemorrhage in the infarcted tissues with tenecteplase.

The 24-h NIHSS outcome was similar between tenecteplase and alteplase in our study. This outcome is a surrogate for recanalisation. One might have expected a greater 24-h NIHSS improvement in the tenecteplase group based on the results of EXTEND-IA TNK [5]. But in the AcT subgroup analysis of LVOs patients, tenecteplase showed similar reperfusion rates on the first angiogram [15]. In the study by Checkouri, there was also no significant difference between tenecteplase and alteplase in the early recanalisation rate of LVO when given as bridging before thrombectomy. But if the thrombus was larger than 10 mm, there was a significantly higher chance of recanalisation using tenecteplase [16].

In our study, the door-to-needle time is shorter in the tenecteplase group. This is likely related to the ease of use as tenecteplase is given as a bolus injection. The improvement in time metrics has also been shown in other studies, with reductions in door-to-needle times and drip-and-ship transfer times with tenecteplase [17, 18]. This is important in the time-critical stroke treatment where time is brain.

We believe that our pragmatic study results can supplement the current literature. Firstly, our suspected LVO patients were diagnosed by clinical criteria and plain CT brain only, and this reflects the situation of hospitals with limited CTA and thrombectomy provision. Secondly, we only studied the effects of intravenous thrombolytic use, without being confounded by mechanical thrombectomy. Even a comparable efficacy and safety profile would mean that tenecteplase should be considered as the treatment of choice, due to its ease of use, translating into improvement in time metrics for patients and nursing staff.

Limitations of this analysis are its small sample size and non-randomised nature. Potential confounding factors might exist. Our clinical suspected LVO criteria might have missed patients with true LVO. And without CTA, some patients without LVO might have been included in the study.

Difference in the percentages of true LVOs in the tenecteplase versus alteplase group might have affected the functional outcome, but it reflects our situation of CTA not being a standard investigation when mechanical thrombectomy is not available. We did not have CTA before or after to assess recanalisation, but instead, early neurological improvement was used as surrogate marker of reperfusion. The period which we started to use tenecteplase coincides with the COVID pandemic. During this period, rehabilitation services were limited, and this might have affected the functional outcome.

Conclusion

In this pragmatic study where clinically suspected anterior circulation LVO patients without thrombectomy were analysed, outcome solely reflects the effects of tenecteplase. Tenecteplase showed comparable safety and efficacy to alteplase in this specific group of patients using clinical criteria. But the result should be interpreted with caution in view of its small sample size and non-randomised study design. This pragmatic study is relevant in regions where access to CTA or thrombectomy might be limited. In the situation of restricted supply of tenecteplase over alteplase, the outcome of this study might support the use of "clinically suspected LVO" criteria, to select patients to be given by tenecteplase instead of alteplase.

Statement of Ethics

This study protocol was reviewed and approved by Central Research Ethics Committee of Hospital Authority, Hong Kong, Approval No. CIRB-2024-058-6. The study has been granted an exemption from requiring written informed consent in view of its retrospective nature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

W.T. Lo: acquisition of data, statistical analysis, interpretation of data, and drafting the article. W.C. Fong: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, and critically revising the article. S.K. Chau, M. Ismail, T.C. Li, C.C. Chan, C.H. Chan, C.Y. Chan, H.F. Chan, L.T. Chan, M.S. Wong, W.Y. Kwok, H.F. Or, S.T. Chan, C.S. Fong, N.G. Chan, and Y.F. Cheung: acquisition of data.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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