MINISTRY OF HEALTH
SINGAPORE

Use of intravenous recombinant tissue plasminogen activator (rtPA) in ischaemic stroke patients

MOH Clinical Guidance

Academy of Medicine, Singapore

College of Family Physicians, Singapore

Chapter of Neurologists, College of Physicians, Singapore

Clinical Neuroscience Society, Singapore

Singapore National Stroke Association

Dec 2013

Levels of evidence and grades of recommendation

Level of evidence

Level	Type of Evidence
1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2^{++}	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies, e.g. case reports, case series.
4	Expert opinion.

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+} .
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}.
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL GUIDANCE

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Contents

Foreword

Stroke is a major cause of death and disability globally. Annually, 15 million people worldwide suffer a stroke and of these, 5 million die and another 5 million are left permanently disabled, placing substantial emotional and economic burden on the family as well as the community.[1] In Singapore, stroke is the fourth leading cause of death, accounting for 9% of deaths in 2012.[2] In addition it is the biggest cause of long term disability. Hence, it is vital that every effort is employed to prevent stroke, and if cases had occurred, to administer evidence-based treatment to achieve the desired clinical outcomes.

This clinical guidance updates recommendations on the use of recombinant tissue plasminogen activator (rtPA) in the treatment of ischaemic stroke, following further development of evidence in this area.

I would like to thank the members of the Workgroup for their work and I hope that these guidelines will be useful in helping doctors and medical professionals in treating stroke patients.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

[1] Mackay J, Mensah GA. The Atlas of Heart Disease And Stroke. Geneva: World Health Organization; 2004
[2] Singapore Health Facts: Principle Causes of Death. http://www.moh.gov.sg/content/moh_web/home/statistics/Health_Facts_Singapore/Principal_Causes_of_Death.html

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

A Intravenous recombinant tissue plasminogen activator (rtPA) is recommended for ischaemic stroke patients within 4.5 hours of stroke onset provided they have no contraindication to thrombolytic therapy. Treatment with rtPA should be undertaken in centres with appropriate facilities and expertise (pg 4).

Grade A, Level 1+

A In patients eligible for intravenous rtPA therapy, treatment should be initiated as soon as possible to optimise the potential benefits and reduce the risks associated with thrombolysis (pg 4).

Grade A, Level 1+

1 Introduction

1.1 Introduction

Recombinant tissue plasminogen activators (rtPA) are thrombolytic agents indicated for use in treatment of acute myocardial infarction, acute ischaemic stroke and pulmonary embolism. The three rtPA drugs available in Singapore are alteplase, tenecteplase and reteplase, of which only alteplase has a registered indication for ischaemic stroke thrombolysis.

The 2009 MOH Clinical Practice Guidelines on Stroke and Transient Ischaemic Attacks included guidance on the use of intravenous rtPA in ischaemic stroke patients. Since then, further evidence has developed on its use and it was necessary to update the guidance. The guidance is intended to assist clinicians managing patients with acute stroke.

1.2 Development of guidelines

An expert workgroup was convened to examine the evidence from a systematic review of the scientific literature on the safety, effectiveness and cost-effectiveness of the use of rtPA in acute stroke, and issue updated guidance. The expert workgroup comprised stroke neurologists from the public and private sector. A literature search was performed to identify clinical studies and systematic reviews examining the efficacy and safety of rtPA in patients within 3 to 4.5 hours of ischaemic stroke. The workgroup deliberated on the findings and made recommendations based on the scientific evidence and their expert judgement.

1.3 Objectives

The main objective of this guidance is to make evidence-based recommendations on the use of rtPA in patients with stroke.

1.4 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. The workgroup advises that the guidance be scheduled for review five years after publications, or when new evidence appears that requires updating of the recommendations.

2 Use of recombinant tissue plasminogen activator (rtPA) in ischaemic stroke thrombolysis

A randomized study of intravenous recombinant tissue plasminogen activator (rtPA) in cerebral infarction demonstrated significant improvement in functional outcome in selected patients treated in specialist units within 3 hours of the onset of ischaemic stroke.[1] Favourable outcomes were achieved in 31% to 50% of patients treated with rtPA, compared with 20% to 38% of patients given placebo. The benefit was maintained 1 year after stroke.[2] Treatment carries the risk of symptomatic brain haemorrhage which is associated with high rate of mortality. Patients with mild to moderate strokes (NIHSS score <20) and persons younger than 75 years of age had the greatest potential for a favourable response to treatment. It is safe and effective in routine clinical practice when used for acute ischaemic stroke within 3 hours of stroke onset in centres with different levels of experience, provided established criteria are strictly followed.[3] The use of streptokinase is contraindicated in view of its lack of beneficial effect on mortality and morbidity.[4]

Another study[5] showed that intravenous rtPA therapy commenced between 3 to 4.5 hours after stroke onset was also associated with a significant increase in favourable outcomes. This study, however, excluded certain subgroups of patients who may respond less favourably to intravenous rtPA therapy. These subgroups include patients with the following characteristics:

a) age >80 years,

b) severe stroke on clinical (National Institute of Health Stroke Scale score >25) or neuroimaging (ischaemic changes involving more than one third of the middle cerebral artery territory) assessments,

c) history of both previous stroke and diabetes mellitus,

d) on treatment with oral anticoagulants.

The benefit achieved with rtPA administered 3 to 4.5 hours after stroke onset was less impressive when compared to previous studies of rtPA treatment administered within 3 hours. Overall within the 4.5 hour window, earlier treatment with rtPA is associated with greater benefit and lower risks.[6]

It is estimated that a clinician would need to treat 3 patients in the 3 hour window following acute stroke onset versus 6 patients in the 3.0 - 4.5 hour window in order for one additional patient to attain a better functional outcome on the modified Rankin Scale.[7]

It is therefore recommended that intravenous rtPA should be initiated as soon as possible but no later than 4.5 hours of stroke onset, with every effort made to minimise the "door-to-needle time" between hospital presentation and initiation of rtPA therapy. It may be necessary to exclude certain high risk patients (as described above) when thrombolysis is administered in the 3.0 to 4.5 hour window.

Other means to extend the time window for intravenous thrombolysis beyond 4.5 hours using novel agents[8] or MR imaging for patient selection have yet to show efficacy.[9]

A Intravenous recombinant tissue plasminogen activator (rtPA) is recommended for ischaemic stroke patients within 4.5 hours of stroke onset provided they have no contraindication to thrombolytic therapy. Treatment with rtPA should be undertaken in centres with appropriate facilities and expertise.

Grade A, Level 1+

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Grade A, Level 1+

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