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Review Article

# PHARMACOLOGICAL TREATMENT OF ACUTE ISCHEMIC STROKE: A REVIEW

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**ABSTRACT**

Stroke is severe neurological disorder characterized by interruption of blood circulation into the brain and the leading cause of serious long-term disability. The central goal of therapy in ischemic stroke is to preserve tissue in the ischemic penumbra, where perfusion is decreased but sufficient to stave off infarction. Therefore, the fundamental treatment of AIS relies on prompt recanalisation and reperfusion of the threatened, but potentially salvageable, ischemic penumbra. Intravenous (iv) thrombolysis with recombinant tissue plasminogen activator (rtPA) remains the current strategy. However, other thrombolysis is underused, owing to various exclusion criteria that limit the number of treated patients. Other thrombolytics are under investigation. Intra-arterial thrombolysis and mechanical thrombectomy devices is also increasingly applied. This review analyses the current status and the problem of the pharmacological treatment of acute ischemic stroke.

**Keywords:** Ischemic, Stroke, Treatment, cerebrovascular, Thrombolytic therapy.

## INTRODUCTION

Stroke is the leading cause of death worldwide and is major cause of morbidity particularly in middle aged and elderly population[1]. According to American Heart Association, definition of stroke is a sudden loss brain function due to disturbance in the cerebral blood supply lasting 24 hr or leading to death. Stroke morbidity and mortality differ widely among countries, being higher in low and middle-income than high-income countries[2]. Stroke incidence and prevalence increase with age and the number is projected to rise with the growing of aged population. Not only stroke is a serious health problem, but also represents a dramatic public financial burden[2].

According to Centers for Disease Control and Prevention, Stroke was the fifth leading cause of death in United States in 2016, and stroke was a leading cause of long-term severe disability[3]. The two main types of stroke are ischemic and hemorrhagic, accounting for approximately 85% and 15% respectively[4]. Numerous conditions are known to increase the risk for stroke, including cardiac disease (coronary artery disease, arterial fibrillation), age, diabetes, hypertension, hypercholesterolemia, cigarette smoking, stress and obesity[5]. Stroke is caused by an abrupt occlusion of an intracranial vessel resulting in decrease cerebral blood flow (CBF) to the brain region supplied. This triggers a complex cascade of pathophysiological events beginning with the failure of energy metabolism and followed by membrane depolarization, protein synthesis inhibition, glutamate release and overstimulation of N-methyl-D-aspartate (NMDA) receptors, $Ca^{+2}$ influx, protease activation with damage to the cytoskeleton and membrane, microglia-activated inflammation, lysosomal membrane rupture with leakage of enzymes leading to cell death [6].

Despite the high prevalence of stroke, there remains limited option for therapy, especially in restoring the lost neurological function. Therefore, investigators are looking for new method to treat ischemic stroke to reduce mortality and reimpose neurological function. Vascular interventional radiology is one of the emerging fields for possibly improving the clinical result of ischemic stroke patient[7].

The fundamental goal of treatment in ischemic stroke is to preserve tissue in the ischemic penumbra, where perfusion is decreased but sufficient to stave off infarction. Tissue in this area of oligemia can be protected by restoring blood flow to the compromised area and optimizing collateral flow. Recanalization, including the administration of intravenous recombinant tissue plasminogen activator (IV r-tPA) and intra-arterial (IA) approaches, attempt to establish revascularization so that cells in the penumbra can be rescued before irreversible injury occurs. Many surgical and endovascular techniques have been studied in the treatment of acute ischemic stroke[8].
This review aims to examine the current status and the future perspective of the pharmacological therapy of acute ischemic stroke.

## TREATMENT OF ACUTE ISCHEMIC STROKE

Assessment of neuronal circuitry loss in typically large vessel occlusions in acute ischemic stroke (AIS) patients led saver to estimate that 120 million neurons, 830 billion synapse and 714 km of myelinated fibres are lost per hour in which there is no treatment. Moreover, each hour the brain loses as many neurons as it does in almost 3.6 years of simple ageing[9].

Therefore, the primary aim of treatments is to restore cerebral blood flow (CBF) as soon as possible, inhibiting the spreading of irreversible injury due to the expansion of the infract core into the

ischemic penumbra. Here, Penumbra refers to a rim of tissue lying just outside the core ischemic region. Within the core ischemic region, oxygen and blood flow is severely reduced, resulting in neuronal death. However, in the ischemic penumbra, cells are viable for short amount of time. The penumbra takes limited amount blood flow from the collateral arteries of the occluded vascular tress[10]. The evaluation of potential stroke patient must be rapid and based on clinical and neurological examination. The most common imaging modalities of parenchymal brain are noncontrast head computed Tomography (CT), which can identify or exude intracranial haemorrhage (an absolute contraindication to fibrinolytic therapy) and Magnetic Resonance Imagimng (MRI). The associated cardiopulmonary complications are addressed and treated. The potency of these interventions has been greatly increases by the establishment of acute stroke units[11].

Thrombolysis is the only therapy approved for acute ischemic stroke. Thrombolysis currently used for Coronary Heart Disease (CHD) and acute pulmonary embolism. For acute ischemic stroke, restoration of blood flow at the occluded artery and restoration of flow to the distal arterial bed are crucial for salvaging the brain tissue in the penumbra, reducing neurological impairment, long-term disability and mortality[12,13].

A thrombus is the final product of the complex blood coagulation process. The clot contains a mesh fibrin and platelets. Thrombolytic drug activate the endogenous antithrombotic system by increasing the conversion of pro-enzyme plasminogen into active protease plasmin, which in turns breaks the cross-links between fibrin molecules. This causes fibrin dissolution and breakdown of intravascular thrombi[14].

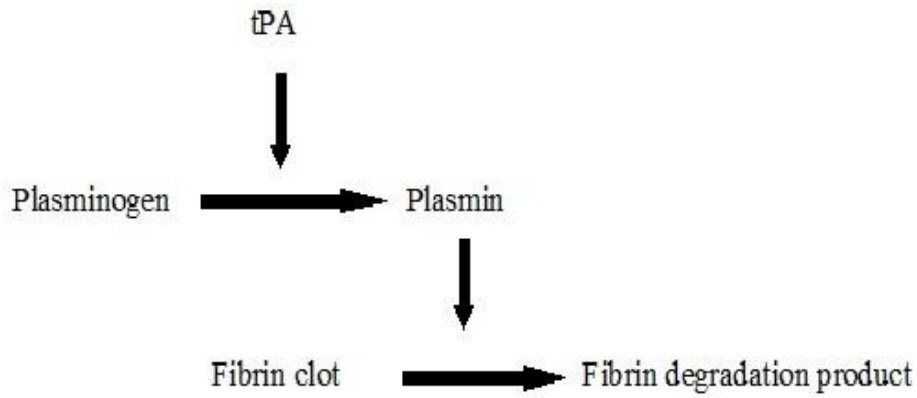


**Figure: Mechanism of thrombolysis**

First generation thrombolytic was streptokinase (no longer used) and urokinase. Second generation thrombolytics include pro-urokinase and alteplase (r-tPA), but pro-urokinase was not approved by the FDA. Third and fourth generation thrombolysis are also being developed. The specificity for bound plasmin enhance from first to fourth generation. Moreover, the more fibrin-selective the protease is the higher is the probability that it stimulate the clot-bound rather than the circulating plasminogen.

**Intravenous Thrombolysis**

Intravenous recombinant tissue plasminogen activator (IV r-tPA) treatment was shown to benefit patients with acute ischemic stroke (AIS) in the 1995 NINDS (National Institute of Neurological Disorders and Stroke) study. IV r-tPA was a major milestone in stroke treatment, as the first disease-modifying therapy for AIS[15]. On the basis of the NINDS study results, in 1996, Food and Drug Administration (FDA) approved the use of IV r-tPA for patients with AIS presenting within 3 hr of symptom onset. Subsequently, in 2008, ECASS (European Collaborative Acute Stroke Study) III has shown the benefit of IV r-tPA over placebo among these treated within 3 to 4.5 hr of symptom onset[16]. These studies established IV r-tPA as a standard therapy for patients with acute ischemic stroke within 4.5 hr of symptom onset. Although the FDA did not modify the original indication for use of IV r-tPA beyond 3 hr, recent stroke guidelines from the American Heart Association (AHA) recommended using up to 4.5 hr from onset of symptoms in eligible patients[17]. Despite this recommendation, the use of IV r-tPA is estimated to occur in <3% of patients presenting with acute ischemic stroke[18]. The narrow therapeutic time window of 4.5 hr is the most common reason that patients do not receive IV r-tPA, along with a few others. Also IV r-tPA has a major therapeutic limitation, including unresponsiveness of large thrombi to enzymatic digestion, resulting in a low Recanalization rate (13% to 15%) in Large Vessel Occlusion (LVO) stroke and a low rate of benefit in the patients having the most disabling stroke. To overcome these major limitations of IV r-tPA, endovascular approaches have been developed over the last two decades using catheters that are delivered intra-arterially (IA) to the site of the intracranial clot to recanalize the occluded vessel[19].

**Intra-arterial Thrombolysis**

The American Heart Association (AHA) guidelines suggest that intra-arterial (IA) thrombolysis can be considered an option for treatment of acute ischemic stroke due to occlusions of the MCA only if given within 6 hr of stroke onset in patients who are not otherwise candidates for IV r-tPA[20].

Prolyse in Acute Cerebral Thromboembolism Trial (PROACT) was the first prospective randomized controlled trial (RCTs) to examine the safety and efficacy of intra-arterial recombinant prourokinase (IA-proUK) and heparin compared with intra-arterial heparin alone, applied within 6 hr of stroke symptom onset in patients with middle cerebral artery occlusion[21]. This phase II study, which randomized 46 patients, showed a significantly higher recanalization rate with IA-proUK along with a significant, but higher symptomatic hemorrhage rate. PROACT II, a phase III study of 180 patients, soon followed and showed the clear superiority of IA-proUK in achieving the primary event of no or slight disability, defined as a modified Rankin scale

(mRS) of 0 to 2 at 90 days, functionally independent outcome in 60% versus 18% ($p<0.001$) of patients as well as a higher recanalization rate of 40% versus 25% ($p<0.04$) correlated with intra-arterial (IA) heparin alone. The improved clinical outcome occurred despite a higher symptomatic hemorrhage rate of 10% in the treatment arm correlated with 2% in control subjects[22]. Despite the success of PROACT II, the FDA did not approve IA-proUK, and soon afterward, this pharmacological agent no longer commercially available. The American Heart Association (AHA) 2005 and 2013 guidelines recommended IA thrombolysis in carefully selected patients with middle cerebral artery (MCA) occlusion within 6 hr who are not candidates for IV r-tPA, but it was enough to make it a standard of care[23].

**Other Thrombolytic Agents**

The urgency for more fibrin-specific agents with larger half-life than alteplase has prompted investigation on third and fourth generation thrombolytic with better pharmacological and pharmacokinetic effect[24]. A third generation, Tenecteplase is a bioengineered variant of alteplase with 80-fold larger resistance to inactivation by plasminogen activator inhibitor-1 and longer half-life[25]. Experimentally, Tenecteplase showed a wider therapeutic in an embolic stroke model in the rabbit than alteplase. In phase-II randomised trial, i.v. Tenecteplase showed significantly greater benefit than i.v. alteplase regarding reperfusion at 24 hrs complete recanalization and clinical outcome. Recently multicentre trial proved the safety and feasibility of tenecteplase in patient with minor strokes[26]. Fourth generation thrombolytic, desmoteplase is a highly fibrin-specific plasminogen thrombolytic agent, is the recombinant version of the plasminogen activator derived from the saliva of a vampire bat[27]. An *in-vitro* study show the variation with alteplase, desmoteplase does not increase blood brain barrier (BBB) permeability. After encouraging results of early phase-II trials, a phase-III trial did not replicate the positive efficacy findings, because possible of methodological factors. Still desmoteplase remain an investigational compound. In conclusion, this novel thrombolytic is still incomplete. Phase-III multicentre trial on safety and clinical outcome are warrented before they can replace alteplace[28].

**Mechanical Thrombectomy**

When thrombolysis is ineffective, mechanical devices are used to recanalize the occluded cerebral vessel to restore the flow. The mechanical embolus removal in cerebral ischemia (MERCI) retriever is a corkscrew-shaped device consisting of a flexible nitinol wire in five helical loops. It allows for placement distally and then en bloc removal of thrombus. The MERCI and Multi MERCI trials evaluated the safety and efficacy in the setting of stroke within 8 hr of symptoms onset[23]. Successful Recanalization was defined as achieving Thrombolysis in Myocardial Infarction (TIMI) score 2-3 flow in the target artery. The device achieved a Recanalization rate of 46%, against a Recanalization rate of 18% seen in historical control subject in PROCAT. Better neurological outcome was achieved in 27.7% of patients, relatively low rate compared with the 60% rate seen in the PROCAT II trial. This led to FDA approved of the MERCI device in august 2004, the first MERCI device approved for the treatment of occluded intracranial arteries. The Multi MERCI trial ensued with the second-generation device and spread on the MERCI trial results, demonstrating a Recanalization rate of 57% with MT only and 69% if used in conjunction with IA r-tPA. The rate of functionally independent outcome (FIO) was 36%, a slight development over the MERCI trial result. The symptomatic rate of intracranial hemorrhage (SICH) was 7.8% in MERCI and 9.8% in Multi MERCI subjects, respectively[29]. Overall analysis of both studies concluded that final recanalization status represents the strongest capable predictor of independent clinical outcome at 90 days in patients undergoing thrombectomy.

In addition, The Mechanical thrombectomy (MT) device for stroke that works by thromboaspiration in occluded intracranial vessels was also developed. The penumbra stroke trial was a single-arm, multicenter, phase II study. The trial enrolled 125 patients with National Institute of Health Stroke Scale (NIHSS) scores of 8 or more, presenting within 8 hr symptoms onset and with angiographic occlusion (TIMI o or 1) of treatable LVO. The study demonstrated successful Recanalization (TIMI grade 2 or 3) in 81.6% target vessels. This led to FDA approval of the penumbra stroke system in January 2008. Again, the rate of FIO was low (25%) in this study, and the SICH was 11.2%[30]. The MERCI and penumbra devices were breakthrough in the field of mechanical thrombectomy, with recenalization rate higher than those seen in the PROCAT trials for IA thrombolysis and with acceptable safety. However, the clinical result of these trials demonstrated relatively low rates of good neurological outcome.

**Anticoagulants Therapy**

Anticoagulants are agent that prevents the formation of blood from forming dangerous clots that could result in stroke. As such, the role of anticoagulants lies in prevention of thromboembolic events, rather than an agent that can develop the outcome of an established vessel occlusion[31]. Data recommended that early anticoagulation with heparin or the low-molecular weight heparins (LMWH)/danaparoid does not lower the risk of early recurrent strokes nor does it that neurological worsening. It also increases the risk of bleeding in the brain or other parts of the body. Hence it is not suggested for use in acute ischemic stroke and should be certainly not given within 24 hr of thrombolytic therapy[20]. Warfarin is globally used as an antithrombotic therapy for patients with TIA or ischemic stroke. Warfarin has been shown to reduce the risk of recurrent stroke or systemic embolism by about 61% in atrial fibrillation (AF) patients with recent TIA or ischemic stroke[32]. Approximately only quarter of patients with ischemic stroke and AF are treated with warfarin. Anticoagulation could be delivered is through use of direct thrombin inhibitor. The drug is given orally fixed dose and found to be at least as effective as dose-adjusted warfarin in reducing stroke with atrial fibrillation[33].

Newer anticoagulants such as apixabin, dabigatran and rivaroxaban have appear and trials on these drug in stroke prevention for patients in atrial fibrillation (AF). Currently, phase III randomised, controlled trials, the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trials, the Rivaroxaban orally once a daily Direct Factor Xa inhibition compared with Vitamin K Antagonism for inhibition of stroke and Embolism in Trial Fibrillation (ROCKET AF), and the Apixaban for Reduction of Stroke and other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial have shown that dabigatran, rivaroxaban, and apixabin are each more efficacious than warfarin for inhibiting stroke in patients with AF, with lower rates of intracranial bleeding[34,35].

Food and Drug Administration (FDA) has been approved dabigatran and rivaroxaban for stroke reduction in people with non-valvular atrial fibrillation[36]. FDA approval for apixabin is still pending. Three studies have compared these three oral anticoagulants for stroke prevention in AF patients[37]. Apixabin was shown to be as effective as dabigatran but rivaroxaban was less effective than dabigatran[37]. Also, apixabin was associated with less major bleeding than rivaroxaban or dabigatran[37]. Dabigatran is more cost effective than rivaroxaban in terms of

acute acre and long-term follow up cost, as well as accrual of quality-adjusted life years [62]. Randomised trials comparing the three drugs are required to confirm these findings. Apixabin was directly compared with aspirin to prevent strokes and shown to be more effective in reducing stroke compared to aspirin in atrial fibrillation (AF) patients who have previous strokes or TIA and who are unstable for or unwilling to take a vitamin K agonist[38].

**Antiplatelet Therapy**

Due to thrombotic origin of AIS and the involvement of platelet aggregation in the development of said thrombus, antiplatelet plays an obvious and pivotal role in the medical treatment. Among the Cyclooxygenase (COX) inhibitors, Oral acetylsalicylic acid administration as monotherapy within 24 to 48 hr after stroke onset is suggested in most patients, although not as a substitute for r-tPA and not as an adjunctive therapy[39]. The high stroke incidence worldwide and ineligibility of many patients to thrombolysis make aspirin a fundamental therapy for ischemic stroke. Dual antiplatelet treatments of aspirin and drugs with different mechanism such as cyclic nucleotide phosphodiesterase inhibitors (cilostazol, dipyridamole) and purinergic receptor P2Y antagonist (clopidogrel) are also safe and effective in reducing stroke recurrence[40].

The observation that the platelet aggregation and thrombus formation require the binding of fibrinogen to platelet through Glycoprotein (GP) IIb/IIIa receptor prompted a series of studies on intravenously administered platelet GPIIb/IIIa receptor antagonist (eptifibatide, abciximab, tirofiban) aimed at preventing plasminogen bridges between platelets, and disintegrating thrombi[41]. However, fibrinogen binding to this receptor is the last step in platelet aggregation; antagonists can inhibit this process whatever is the agonist. Experimental studies in animal stroke model had shown that the combination of a GPIIb/IIIa receptor antagonist with tPA prevent infarct volume and improved neurological outcome more actively than the tPA alone[42].

However, in clinical trial this combination seemed to be a double edged sword enhancing both recanalization and risk for symptomatic rate of intracranial hemorrhage (SICH). More phase III randomised clinical trials (RCTs) are clearly required before these agents are approved[39]. The multicentre, double-blind, randomised phase II trial Combined Approach to Lysis Utilizing and r-tPA in Acute Ischemic Stroke-Enhanced Regimen trial (CLEAR-ER) sponsored by the NIH/NINDS indicate the safety (in terms of SICH events) and efficacy (mRS) of the combination or decrease dose r-tPA (0.6 mg/kg) and eptifibatide compared with full-dose alteplase (0.9 mg/kg) alone[43]. This studycan be regarded as hypothesis-generation, recommending a phase III further investigation.

**Antihypertension Therapy**

Hypertension is common in patients admitted (defined as BP>140/>90 mm hg) for an acute ischemic stroke, and a transient blood pressure rise can be found also in previously normotensive patients. It is probably linked to lesions of particularly cerebral areas causing impaired neurogenic cardiovascular control, dysautonomic regulation, and a reflex response to cerebral ischemia[44]. Hypertension increases the risk of cerebral oedema and hemorrhagic transformation of AIS. Small percentage patients are hypotensive and could be at risk of further ischemia damage due to reduced CBF in the ischemia penumbra. Hypotension may be due to hypovolaemia, septic shock and other cardiovascular incidents which require prompt treatment. Hypotension, hypertension and BP variability are independently associated with worse clinical outcome and enhance mortality[45].

The evidence recommended that anti-hypertension treatment reduce stroke and TIA, the benefit of BP lowering in acute ischemic stroke is controversial. Pathophysiology would argue against overly intensive BP lowering since it could lead to the impairment of the collateral perfusion of the ischemia penumbra and to increase infarction[46]. Experimentally, the studies on stroke models in spontaneous hypertension rats showed the benefit of pretreatment with anti-hypertension (AH) drugs. Angiotensin II receptor blockers (ARBs) tended to be more effective than other classes of anti-hypertension[47]. The angiotensin-II receptor blocker (candesartan) administered after reperfusion in an animal model of stroke in rats (middle cerebral artery occlusion, MCAO) rapidly decreased BP, reduced the neurovascular injury and improved outcome[47].

Clinically, numbers of studies have assessed the effect of various anti-hypertension agents including β-receptor antagonists, angiotensin converting enzyme inhibitors (ACE inhibitors). ARBs, calcium channel blockers (CCB), and nitrates, the results are disappointing. Cochrane Systematic Review of 26 RCTs on five classes of anti-hypertension with different routes of administration showed that BP lowering did not reduce mortality at the end of trial or dependency[48].

In this context of insufficient evidence, the Guidelines suggested the following: (1) for hypertension patients for thromobolysis, the anti-hypertension treatment should be started if BP is ≥185/110 mm hg with the target of maintaining ≤180/105 mm hg. Treatment with either the $\beta_1$-receptor antagonist labetalol or the CCB nicardipine is suggested; (2) patients who not receive thrombolysis should not be treated with anti-hypertension unless BP is >220/120 mm hg; (3) treatment of hypotension with a vasopressor (phenylephrine) to improve CBF only in exceptional cases[39]. Hence, three decade following the first discussion on this subject, the debate on blood pressure (BP) treatment in acute ischemic stroke is far from over. The target remains findings a balance between the need to reduce the injury of ischemic and preserve perfusion pressure.

**Antioxidant Therapy**

Antioxidants are molecules which scavenge the free radicals or reactive oxygen species (ROS) and stop the chain reaction[49]. Free radicals production is increased in both the ischemic core and penumbra following stroke injury, and this is believed to cause enough damage seen in this zone. There are many agents that either inhibit free radical production or block its activation that have been shown to be very powerful in experimental models. Uric acid is well established natural antioxidant present in fluids and tissue. Administration of uric acid (UA) resulted in a extensive and significant reduction in ischemic damage and improved behavioral outcome[50]. Tetramethylpyrazine, edaravone, alpha-phenyl-N-tert-butyl-nitrone, NXY-59 and FR210575 are some of other free radical inhibitors that have been shown to be potent against experimental ischemic injury[51]. Finished clinical trials with free radical scavengers, however have limited success after acute ischemic stroke. The NXY-59 was initially reported to be potent in acute ischemic stroke, however a follow-up trial in a larger cohort of patients failed to demonstrate potency[52]. EGb-761, being discovered by Ipsen, is a free radical scavenger derived from a concentrated extract of Ginkgo[53]. that has recently completed a phase-III clinical trial with results still pending.

**Anti-apoptotic Agents**

Apoptosis occurs via caspases-dependent as well as caspases-independent mechanism. Caspases are protein-cleaving enzymes that belong to a family of Cysteine aspartases constitutively expressed in both adult as especially newborn brain cell, particularly neurons[54]. The evidence suggests that apoptosis contribute to neuronal cell death in stroke. Caspases divided into three groups (I, II, and III), are essential players in apoptotic neuronal cell death[55]. Various groups studied the effects of caspases inhibition on cerebral ischemia-induced neurodegeneration by using the broad spectrum caspases inhibitor z-VAD, either in the dichlorobenzoyloxopentanoic acid (dcb) or fluoromethylketone (fmk) form and z-DVED-fmk. Both inhibitors are neuroprotective in mouse model in the rat[56]. Ac-YVAD-cmk is caspases group I inhibitors, also was shown to be neuroprotective in a mouse transient model of cerebral ischemia[56]. Strategies to silence caspases or suppress apoptosis associated to gene products using antisense oligonucleotides or viral vector-mediated gene transfers substantiate this observation. However, caspases inhibitors do not decrease infarct size in all brain ischemia models. This might relate to the intensity and duration of ischemia[57]. To date however, the potency of anti-apoptotic agents in human stroke patients has not yet been tested.

**NMDA receptor Antagonist**

Many compounds that interfere with glutamate receptor activation have been developed therefore and tested against human clinical trials and experimental animal model of stroke. NMDA receptor antagonists can be used for the treatment[58]. The noncompetitive NMDA antagonist MK-801 is use to prevent NMDA receptor dependent influx of calcium[59]. BQ-869, a potent NMDA receptor antagonist, blocks the receptor in concentration-dependent in focal cerebral ischemia in mouse model and reduced stroke mortality[60]. Both MK-801 and dextromorphan, another noncompetitive NMDA antagonist exerts protective effects in experimental studies[59], but clinical trials were completed early because of phencyclidine-like psychotic side effect and poor efficacy against stroke.

Many NMDA receptor antagonists are presently in phase II and III clinical trials. Most clinical trials involving NMDA receptor antagonists have failed due to unwanted side effect of the drugs; since the receptors also play an important role in glutamatergic neurotransmission; blocking them causes side effect[60]. Non-NMDA antagonist have also been developed and studied against stroke. YM-872 is an AMPA antagonist tested in human phase II clinical trials[61]. In addition, another AMPA antagonist, SPD-502, as well as metabotropic glutamate receptor modulators are being developed and tested against stroke in human and animal[62]. However, the development of NMDA receptor antagonist against stroke has thus far been disappointing.

**Anti-inflammatory Agents**

Inflammation in stroke is characterized by the accumulation leukocyte and activation of resident microglial cells. Inflammatory cells can contribute to stroke pathology mechanisms. They form accumulation in the venules after reperfusion and exacerbate cell death through production of free radicals and cytokines[63]. Cell adhesion molecules such as integrins, selectins, and ICAMs permit endothelial-inflammatory cell interactions. Treatment with anti-selectins antibodies successfully decreased infarct volume by up to 70% after transient focal ischemia (TFI) in mice[64]. Also anti-ICAM-1 has decrease infarct size[65]. Recently, a phase II trial using anti-CD11b/CD18 agent UK-279276, has been completed, and demonstrated that this compound is safe and well-tolerated[66]. Other target include the mitogen activated protein kinase (MAPK), which have been linked to inflammatory cytokine production and cell death in ischemic stroke. SB-239063 is a MAPK inhibitor that decreases infarct size and improved neurological outcome following focal stroke in rodents, which may be used alternative target in inflammation of human stroke patients[67]. Matrix metalloproteinases (MMPs) inhibitor such as BB-94 and KB-R7785 reduced the infarct volume in treated mice after permanent focal ischemia[68]. MMP inhibitors have been evaluated in patients for their anti-angiogenic properties and well tolerated[69]. Although chemokines can have pro or anti-inflammatory actions, the effect of chemokine up-regulation in ischemia reperfusion injury is detrimental. Various, other anti-inflammatory cytokine approaches were tested in experimental stroke models, along with several antibodies that target inflammatory proteins. However, there have been no successful clinical trials of such anti-inflammatory agents reported so far.

**CONCLUSION**

The past decade has been seen extraordinary advance in the treatment and prevention of stroke. However, the evidence points to IV r-tPA therapy within 4.5 hr from stroke onset remains the mainstay of acute ischemic stroke, although far from ideal. Various alternative strategies and agent have been extensively investigated to enhance the percentage of patients treated, improve outcome and lower SICH (symptomatic intracerebral haemorrhage). Despite this, recanalisation treatment as described is flourishing at a rapid rate and more emphasis and interest are being directed at these areas. Although vessel recanalisation is vital to enhancing the possibility of significant tissue reperfusion, clinical trials need to emphasis functional outcome rather than reperfusion/recanalisation rates to adequately assess success of these device.

In addition, education of emergency medical staff personally is also crucial in enabling faster referral to a unit where thrombolysis can be done. This approach at present will halt to some extent the stroke pandemic that we are facing. Public profliling of stroke will strongly assist in dealing with risk factors and implementation of preventive strategies. These requirements will continue to be necessary, if not more so, as new development become established, such as MRI-based patient selection, intra-arterial or neuroprotectants. In order to large number of patients will still present too late for irreversible brain injury. Such patients require rehabilitation and psychological method. Prevention remains the more reasonable strategy and should be actively pursued worldwide by tackling the risk factors for ischemic stroke.

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