REVIEW ARTICLE

Clinical Efficacy of Piracetam in the Management of Acute Stroke and Post-Stroke Sequelae: An Expert Panel Review and Opinion

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ABSTRACT

Stroke is a major cause of death worldwide. Prompt treatment and decision-making is essential for good outcomes. The two major therapeutic approaches for acute ischemic stroke are thrombolytics and neuroprotectants. Piracetam, a nootropic drug aims to increase cerebral blood flow, enhance oxygen extraction, restore membrane fluidity and modulate neurotransmission. Likewise, citicoline has been shown to positively influence cerebral plasticity and neurorepair processes. The present article aims to offer insights on the current management of acute stroke and to position piracetam and its combination with citicoline in the management of acute stroke and post-stroke sequelae based on an expert panel discussion.

Keywords: Citicoline, neuroprotectants, piracetam, thrombolytics, stroke

Stroke, described as a clinical syndrome comprising of rapidly emerging clinical signs of focal disturbance of cerebral function for more than 24 hours or resulting in death with no apparent cause other than a vascular origin, is the second leading cause of death globally.[1,2] It is estimated to be the third most common cause of disability worldwide.[1] The prevalence of incident strokes, stroke-survivors, stroke-related deaths and disability-adjusted life-years is escalating extensively.[2] Stroke can be broadly classified as ischemic stroke, accounting for 68% of all strokes and hemorrhagic stroke constituting 32%.[1] This article aims at describing the management of stroke and the positioning of piracetam and its combination with citicoline in the management of acute stroke and post-stroke sequelae.

METHODS

In 2021, two expert group meetings were conducted virtually involving 29 neurologists from various cities in India namely, Hyderabad, Delhi, Kolkata, Mumbai, Patna, Bangalore, Varanasi, Chennai, Madurai, Coimbatore, Lucknow, Amravati, Vizag, Pune, Siliguri, Jamnagar, Pilibhit, Sangli, Durg, Rohtak and Bhopal. The main purpose of these meetings was to discuss and understand various aspects of managing acute stroke with an emphasis on the clinical role of piracetam and its combination with citicoline.

MANAGEMENT OF ACUTE STROKE

Every minute, atypical patient with ischemic stroke loses 190,0000 brain cells, while approximately 14000,000,000 nerve connections are damaged and 7.5 miles of nerve fibers are lost.[1] Hence, a condition like stroke requires prompt treatment and decision-making, and round-the-clock preparedness for hospitals to ensure evidence-based care, which is crucial for good outcomes in stroke. Revascularization and limitation of secondary neuronal injury are the prime goals of advanced stroke management.[3] Two major types of therapeutic approaches to acute stroke are: 1) Thrombolytics to restore cerebral blood flow; 2) Neuroprotectants to target cellular pathways to preserve brain function, enhance neuronal repair and promote recovery. The present effective treatment modalities for acute ischemic stroke are intravenous thrombolytic therapy within 4.5 hours of onset and intra-arterial thrombectomy within 6 hours of stroke onset.[4]

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Adjunctive treatments delivered in combination with intravenous thrombolysis for ischemic stroke, either pharmacological or nonpharmacological, provide an array of therapeutic effects, including anti-inflammatory, antiexcitotoxicity, antioxidizing cerebral metabolism reducing and apoptosis-adjusting effects.[5,6] Thrombolysis therapy enhances the therapeutic effect of neuroprotective agents, as oxygen and nutrient supply restored after thrombolysis are the prime factors for neuronal survival. The neuroprotective action will be augmented once the occluded artery is reopened, as neuroprotective agents partially work by lowering the ischemia-reperfusion injury. Moreover, neuroprotectants utilized as adjunctive therapy also have the potential to attenuate ischemic injury in the penumbra area, lengthen the thrombolytic time window and lower the risk of symptomatic intracranial hemorrhage by stabilizing the blood-brain barrier.[6] Currently used nootropics include pyrrolidinone derivatives like piracetam, oxiracetam, aniracetam and promiracetam as well as natural products like *Ginkgo biloba, Bacopa monnieri, Rhodiola rosea,* etc.[7] The other adjuvant pharmacological therapies include those that preserve blood-brain barrier (e.g., atorvastatin, batimastat, candesartan, cilostazol, fasudil, minocycline, etc.), improve vascularization, protect the cerebrovasculature (e.g., coumarin derivate IMM-H004 and granulocyte-colony stimulating factor) and deploy their effects through other mechanisms of action (e.g., oxygen transporters, ascorbic acid, etc.).[5] The nonpharmacological therapies include stem cell treatments, gas therapy, hypothermia and remote ischemic conditioning with multidimensional biological effects.[5,6] Figure 1 illustrates the algorithm for multimodal management of stroke.[8,9]

Consensus Opinion 1

The National Institutes of Health Stroke Scale (NIHSS) is used universally for all patients to assess the severity, apart from computed tomography (CT), angiography and magnetic resonance imaging (MRI).

The levels of inflammatory markers, C-reactive protein (CRP) and D-dimer levels should be measured and anticoagulant and antiplatelet medications must be prescribed to patients.

POSITIONING OF PIRACETAM IN MANAGEMENT OF ACUTE STROKE, POST-STROKE APHASIA AND OTHER CONDITIONS

Piracetam, the first nootropic drug, is a cyclic derivative of the neurotransmitter gamma-aminobutyric acid (GABA). Although the mode of action has not yet been fully elucidated, studies have reported that it influences neuronal and vascular functions. Its neuronal effects include an impact on neurotransmission by influencing cholinergic, serotoninergic, noradrenergic and glutamatergic systems. Piracetam has been found to increase the number of post-synaptic receptors and restore their function.[10] Additionally, it offers neuroprotective effects by restoration of neurotransmission and improvement of metabolism. The anticonvulsant effects of piracetam have been shown to reduce seizure severity and enhance anticonvulsant action of other drugs such as carbamazepine and diazepam. Its vascular effect is translated by an antithrombotic effect leading to improvement of microcirculation and decreasing platelet aggregation.[10,11]

In congruence with its numerous pharmacological effects, piracetam has documented efficacy in a diverse range of indications. Piracetam is indicated in the management of vertigo, dyslexia, cortical myoclonus and sickle cell anemia in addition to age-related cognitive disorders. It is a well-tolerated drug and its benefits in these conditions appear to result from an array of neuronal and vascular effects associated with restored membrane fluidity.[10]

The basis for the use of piracetam in acute stroke is the combination of its neuroprotective, hemorheological and antithrombotic properties. Piracetam has been shown to increase compromised regional cerebral blood flow in patients with acute stroke and to improve clinical outcomes when administered soon after symptom onset.[12]

A hospital-based observational study by Chen et al evaluated the association of piracetam use and the clinical characteristics of NIHSS changes in patients enrolled based on 2,483 stroke registration data cohorts. Multivariate analysis showed significant improvement in NIHSS scores with piracetam use. Subgroup analysis revealed the efficacy of piracetam in the following patient groups: age ≥75-year-old, male gender, normal weight, obesity, ex-smokers, patients with hypertension, dyslipidemia, without diabetes mellitus and without atrial fibrillation. Thus, selection of clinical characteristics under which piracetam treatment should be given is important for NIHSS improvement of ischemic stroke patients.[4]

Aphasia is a common symptom following a stroke.[13] Studies on piracetam in post-stroke aphasia patients have shown elevation of cerebral blood flow and glucose metabolism in infarcted and penumbral tissues and to be an effective adjunct of verbal skills.[4] Piracetam

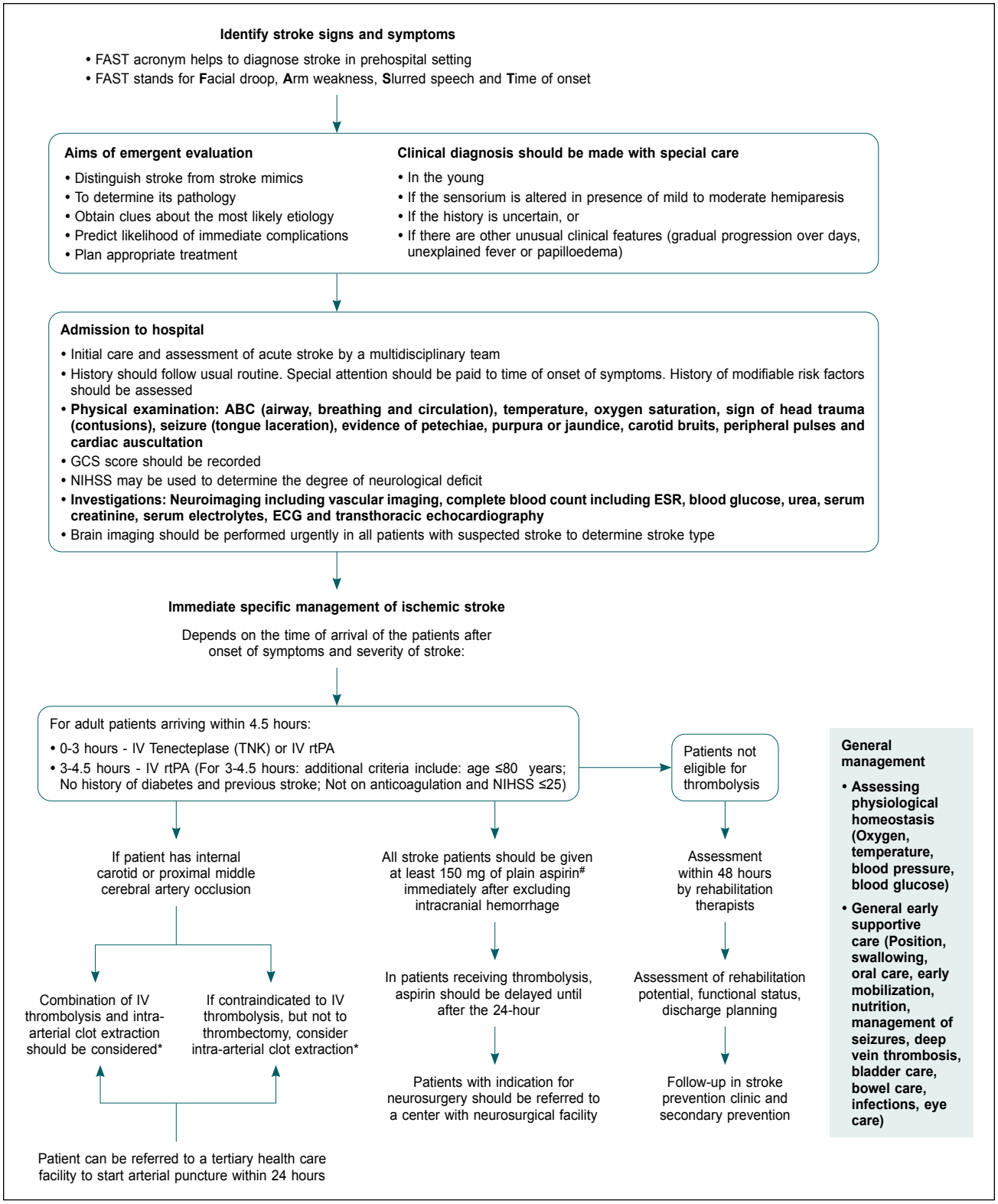

Figure 1. Multimodal management of stroke algorithm (Developed from: Guidelines for prevention and management of stroke 2019; Van Bussel EF, et al.).

*If they have internal carotid or proximal middle cerebral artery occlusion causing a disabling neurological deficit.

#Patients with acute ischemic stroke who are allergic to or intolerant of aspirin should be given an alternative antiplatelet agent (e.g., clopidogrel).

GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale; ESR = Erythrocyte sedimentation rate; rtPA = Recombinant tissue plasminogen activator.

in combination with speech and language therapy has the potential to facilitate rehabilitation from acute and chronic aphasia, indicating clinical support for its use in post-stroke aphasic patients.[13]

Consensus Opinion 2

Piracetam has a role in the management of acute stroke in effectively improving NIHSS and Barthel index in stroke patients. It also has a definitive role in long-term treatment of patients with post-stroke aphasia. Table 1 provides an overview on the dosage regimen of piracetam in acute stroke and post-stroke.

POSITIONING OF PIRACETAM AND CITICOLINE COMBINATION IN THE MANAGEMENT OF ACUTE STROKE, POST-STROKE APHASIA AND OTHER CONDITIONS

With several overlapping processes leading to either damage or protection, the pathology of stroke is complex. Even if substantial neuroprotection can be achieved by aiming at just one of these processes, the probable benefit is even more if various mechanisms of damage can be repressed at the same time. Accordingly, combination therapy with more than one drug has proven to be effective in multiple experimental studies.[14]

Citicoline, a drug that provides neurovascular protection and repair effects with an excellent safety profile, is indicated in patients with acute ischemic stroke and other neurological disorders. A meta-analysis of trials of citicoline in acute and subacute stroke suggested a beneficial and substantial treatment effect, with absolute reductions of up to 12% in the rates of disability and long-term deaths. The odds ratio was 33% higher compared to the placebo with respect to the complete functional and neurological recovery in patients with moderate to severe acute ischemic stroke treated with oral citicoline for 6 weeks.[15] The effect of citicoline is correlated with the mechanisms that regulate cerebral plasticity and neurorepair processes. Based on its therapeutic effect, citicoline is used in the management of several nervous system dysfunctions which include dementia, memory loss, depressive disorders and Parkinson's disease.[16]

Combination of citicoline and piracetam can be a beneficial option in the management of various cognitive disorders. As the combination can cross the blood-brain barrier, it can easily enter the cerebrospinal fluid of the brain. The combination can be used in memory enhancement, neurological and cognitive disorder, Parkinson's disorder, Alzheimer's disorder, depression and anxiety, closed craniocerebral trauma, dyspraxia clotting, coagulation and vasospastic disorders.[17]

Consensus Opinion 3

Piracetam and citicoline can be used as sequential therapy or combination therapy for stroke or post-stroke aphasia.

Oral piracetam can be started at 1.2/2.4/4.8 g per day and titrated as per response followed by 1 g per day citicoline or vice versa for 3 to 4 weeks and maintenance of either of the drug for a longer duration (or at least 9-12 months) or combination therapy as mentioned in Table 2. Both the drugs are safe for long-term use.

In the Indian scenario, there exist some discrepancies of opinions regarding the use of piracetam and citicoline in the management of acute stroke as their definitive role in patients with acute stroke requires additional exploration. There is a need of strong clinical data support of piracetam and its combination with citicoline to establish its efficacy in acute stroke.

STROKE AND IMPACT OF COVID-19

Coronavirus disease 2019 (COVID-19) infection has been linked with an increased risk of ischemic stroke. A 10-fold elevated incidence of ischemic stroke during the 14 days after COVID-19 diagnosis as compared with the control interval was reported. Even when the risk interval was extended to 21 and 31 days after COVID-19 diagnosis, the incidence of ischemic stroke remained significantly high.[18] Moreover, severe COVID-19 disease

Table 1. Dosage Regimen of Piracetam in Acute Stroke and Post-Stroke

Indications	Dosage regimen based on expert opinion
Acute stroke	Within 12 hours of presentation, piracetam 12 g IV bolus administered over 20 minutes followed by 3 g 6 hourly IV for 3 to 5 days as per response and followed by oral maintenance therapy for 1 to 3 months.
Post-stroke	Piracetam 1.2 to 2.4 g per day orally for a longer duration or at least 9 to 12 months.

IV = Intravenous

Table 2. Dosage Regimen of Piracetam and Citicoline Combination in Acute Stroke and Post-Stroke

Indications	Dosage regimen based on expert opinion
Acute stroke	Piracetam can be started with 1.2/2.4/4.8 g as per response followed by 1 g citicoline for 3 to 4 weeks.
Post-stroke	Combination of piracetam 800 mg and citicoline 500 mg twice a day orally for 1 to 3 months.

occurred more frequently in elderly patients who are more likely to have multiple comorbidities; these patients also are more susceptible to incidence of strokes.[19] Cytokine storm development, innate immune system stimulation, propagation of embolic events by existing or new-onset arrhythmias, hypoxia-induced ischemia ancillary to severe pulmonary disease, thrombotic microangiopathy, endotheliopathy/endothelialitis and multifactorial activation of coagulation are the key proposed mechanisms of COVID-19 associated stroke. Literature supports raised levels of D-dimer in COVID-19 infected patients experiencing an acute ischemic stroke, signifying activation of the coagulation and innate immune system. A cytokine storm leading to increased levels of both interleukin-6 and CRP is considered to be associated with the risk of stroke in COVID-19 patients.[19]

The "Indian Stroke Association" had issued a consensus statement to provide a treatment model for patients who have suffered a stroke in the pandemic. In a positive or suspected COVID-19 patient, rapid screening should be done in the screening areas for patients presenting with stroke; evaluation and management should be undertaken without delay. Taking into account the time sensitive nature of the disease, the primary contact hospital can consider managing the patient in the acute phase of stroke; in case shifting of the patient is not possible to the designated COVID-19 hospital on time. The patient could then be referred to the designated COVID-19 hospital as soon as possible with prenotification and a suitable transfer method.[20]

Consensus Opinion 4

The prevalence of stroke has increased since the COVID-19 outbreak. The incidence of acute ischemic stroke was about 1% to 2% in practice since the outbreak. This increase in prevalence was due to the deranged lifestyle changes, decrease in regular follow-up visits due to ongoing restrictions, COVID peaks and due to COVID-19 infection directly. In COVID-19 positive patients with 2 or more weeks of pulmonary symptoms, and individuals who have recovered from COVID-19, there is increased presentation of stroke, which can be attributed to the increased pro-inflammatory cytokines and increased risk of thromboembolism with or without haemorrhagic component.

CONCLUSION

Prompt treatment of stroke can prevent long-term disability and death. Management of stroke comprises of a multidisciplinary approach that starts and extends beyond hospital admission. Piracetam, a nootropic drug, with its several neuronal and vascular effects, has proven beneficial in several conditions including age-related cognitive disorders, vertigo, cortical myoclonus, dyslexia and sickle cell anemia. Combination of piracetam with citicoline–a drug that combines neurovascular protection and repair effects, can be potent in the management for various cognitive disorders. Literature supporting the benefits of piracetam and citicoline in the treatment of cognitive disorders are numerous, although potential beneficial effects of piracetam and its combination with citicoline remain unclear in stroke patients because of insufficient well-controlled studies.

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Conflict of Interest

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Study: Alzheimer's Genes Might Increase Risk of Epilepsy

Research published in *Neurology* stated that persons who have a genetic tendency for Alzheimer's disease might have an increased risk of epilepsy, and those who have a specific form of epilepsy may have an increased chance of getting Alzheimer's disease.

Researchers examined gene variation throughout the human genomes of 1,11,326 people with Alzheimer's disease and 6,77,663 people without the condition using a genome-wide association analysis. They utilized a study strategy known as Mendelian randomization to see if there was a link between genetic variants and epilepsy risk.

Alzheimer's disease was shown to be associated with a 5.3% greater risk of generalized epilepsy and a 1.3% increased risk of localized epilepsy with hippocampal sclerosis. They also discovered that genes that indicated a lesser level of an Alzheimer's disease biomarker were associated with an increased likelihood of generalized epilepsy.

Experts say those with focal epilepsy and hippocampal sclerosis is roughly four times more likely to acquire Alzheimer's disease than people without epilepsy. (*Source:https://theprint.in/science/having-alzheimers-genes-may-increase-risk-of-epilepsy-study/1593410/*)