

Review Article

A review of role of uric acid in acute ischemic stroke: changing trends

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ABSTRACT

Uric acid, a powerful and potent antioxidant. Effect of uric acid in acute stroke was a controversy. Chronic hyperuricemia is atherogenic. But in recent days various articles were published about the antioxidant and the beneficial effects of uric acid due to cerebral antioxidant effect. In this article, we had reviewed various articles which discuss the major beneficial and deleterious effect of uric acid in neurological diseases to conclude the effect of uric acid in the scenario of acute ischemic stroke. This review was conducted through an Internet search on a public access website like PubMed, Google Scholar, Cochrane library, ProQuest and Medline databases until 2019. Keywords utilized included uric acid (UA), Acute ischemic stroke, neuroprotection, stroke therapy, and vasculoprotection. Total of 10 article from literature was reviewed, the major exclusion criteria were the studies that included patients which coronary artery disease, chronic kidney disease, Metabolic syndrome and patients who are taking drugs that influencing the uric acid levels. Chronic hyperuricemia is atherogenic and it had a negative impact on outcome in stroke, but in acute setting recent days various papers had been published about the beneficial effect of uric acid due to its antioxidants property. This was further supported by the co administration of Intravenous uric acid along with thrombolysis for acute ischemic stroke. Hence, we had concluded that, uric acid had a beneficial effect in a setting of acute ischemic stroke.

Keywords: Acute ischemic stroke, Antioxidant, Cerebrovascular accident, Hyperuricemia, Neuro-protective, Uric acid

INTRODUCTION

Stroke is one of the most common and leading causes of morbidity and mortality in the world. Even after the tremendous advances in the management of acute ischemic stroke patients about one-third of the cases had a severe disability and one third succumbed to death. Hence nowadays prime importance was given to find out the agents which had a Neuro-protective effect thereby reducing the neuronal damage and resulting in a better clinical outcome. Even though various factors influence the outcome in acute ischemic stroke, most of them were non-modifiable like age, sex, prior stroke, comorbidities

like diabetes, hypertension.¹ Very less modifiable factors influence the outcome of patients with acute ischemic stroke. Most of it was associated with the treatment aspect of stroke like reperfusion therapies like thrombolysis and mechanical thrombectomy.² Nowadays various newer treatment modalities were emerging mainly targeting the targets involved in the pathophysiology of stress-induced neuronal damage which ultimately resulting in reduced neuronal damage.

Uric acid, an end product of purine metabolism. Uric acid, a powerful and potent antioxidant available in the humanbody.³ A wide view of controversy is present in

the role of uric acid and its effect in acute ischemic stroke. It is widely accepted that chronic hyperuricemia is atherogenic and leads to increased cerebral damage and a high amount of neuronal loss.⁴ But in recent days various articles were published about the antioxidant and the beneficial effects of uric acid in neurological diseases predominantly secondary to the extensive cerebral antioxidant effect.

In this article, authors had revised various articles which discuss the major beneficial and deleterious effect of uric acid in neurological diseases to conclude the effect of uric acid in the scenario of acute ischemic stroke.

REVIEW OF LITERATURE

A stroke is defined as a syndrome of quickly developing neurological signs of focal or global neurological dysfunction pertaining to a vascular territory with no other apparent cause.⁵ Usually, symptoms to say it as stroke should last for more than 24 hours or it may progress to death. Stroke is broadly classified into ischemic stroke and hemorrhagic stroke and among them, 68% proved to be ischemic and the remaining 32% was found to be hemorrhagic.⁶ The prevalence of stroke in India is about 84-262/100,000 - rural areas, 334-424/100,000 - urban areas⁷. And it was found that stroke accounts for about 10% mortality in a developed country and still higher in a developing country and they have also found that these figures are going to increase in the future because of the burden of risk factors like smoking, diabetes, hypertension, and other modifiable risk factors.⁷

The incidence, prevalence, geographical distribution, and the clinical outcome were different from the patient with stroke who is young which is called a young stroke. Among the total burden of ischemic stroke, stroke in young contributed about 10-15% and it causes significant morbidity and substantial mortality which has to be seen and taken into consideration so that appropriate measures are taken.⁸ In the past even though there are many modifiable and non-modifiable risk factor were identified but still, that list is increasing and most of the newly identified risk factor is being used, studied and under research for use as a therapeutic target. Most of the risk factors were studied in a multicenter trial called interstroke study. In which Diet, waist-hip ratio, psychological stress, depression, binge drinking and most importantly the ratio of apolipoprotein B to A1 were given special importance.⁹ And also atrial fibrillation substantially increases the stroke in the given population as much as 23.5%.¹⁰

URIC ACID

Uric acid is an end product of normal purine metabolism in our body and hence a constant amount of uric acid is produced. The main organ that is concerned with the regulation of uric acid is the kidney. About 90% of all the filtered uric acid in the glomerulus will be reabsorbed by

the tubules. So, any factor that increases the purine metabolism will increase the uric acid and also not to be forgotten is the dietary factor, high consumption of purine containing products will also increase the uric acid levels. The normal serum uric acid level in males and females is different and it is comparatively low in the female when compared to males this is mainly because of the increased renal excretion of urate which is attributed preliminarily secondary to the increased oestrogen levels.¹¹ The exact biological effects of uric acid is still a controversy since it has both harmful effects and beneficial effects.

Biological effects of uric acid

The harmful effects of uric acid are well known, and it is known to cause various deleterious effects on human beings. The well known deleterious effects of uric acid were it contributes to Gout, urolithiasis, nephrolithiasis. The risk of nephropathy was about 20-30 increased when compared to individuals with normal value.¹² It is also well known that the relationship between the incidence of nephropathy and uric acid, it was now found that both acute nephropathy and chronic nephropathy can occur due to elevated uric acid. Johnson et al had found that uric acid has a direct pathological relationship with the occurrence of nephropathy which is mainly due to the occurrence of chronic interstitial damage which ultimately leads to chronic tubulointerstitial nephritis.¹³

It was a well-known fact that hypertension leads to hyperuricemia but nowadays recent researches were proving that chronic hyperuricemia will ultimately be leading to hypertension this was initially proven in rats which are administered with a drug which inhibits uricase and leading to hyperuricemia and they had found that those rats which developed hyperuricemia ultimately developed hypertension. This was further supported by the reduction of serum uric acid levels with the usage of xanthine oxidase inhibitor also resulted in control of blood pressure.¹⁴⁻¹⁶

Uric acid and cardiovascular events

The effect of uric acid in the cardiovascular and cerebrovascular disease was debatable and still yet not fully evaluated and various studies were done which showed increased uric acid, independently act as a poor marker and increases the mortality and morbidity in cardiovascular and cerebrovascular events.^{17,18} On contradictory to this MRFIT study showed a poor and weak relationship between the uric acid and CV outcomes.¹⁹

Uric acid in acute ischemic stroke

Endothelial cell in ischemic stroke

The vascular endothelium cells were very important in organogenesis and its function starts before the genesis of

blood vessel perse. In the central nervous system, the vascular endothelium predominantly in the brain acts in maintaining cerebrovascular resistance which plays a major role in reducing the injury during cerebral ischemia. Endothelial cells in normal circumstances also determine the thromboresistance property and thereby suppressing the pro-inflammatory process and reducing the incidence of atherosclerosis.²⁰ Endothelial cell also maintains the resting tone of the cerebral blood vessel and thereby regulating the cerebral blood flow. These various mechanisms contributes to the endothelial dysfunction as the main Conner stone in the pathogenesis of neuronal injury during the ischemic stroke and also makes the endothelial cell as the therapeutic target.

The endothelial dysfunction in ischemic stroke is mainly attributed to oxidative stress and that is mainly constituted by reactive oxygen species and reactive nitrogen species. These reactive oxygen and nitrogen species were abundantly produced in the injured zone for about 6-12 h after stroke onset which facilitates the expansion of ischemic penumbra predominantly by lipid peroxidation, protein nitration, mitochondrial damage and oxidation which ultimately lead to depletion of the antioxidants leading to neuronal damage by, activation or inhibition of various signaling pathways and disruption of blood-brain barrier.²¹

Uric acid - an antioxidant

In recent days the antioxidant property of uric acid was studied extensively, and many papers were published regarding the antioxidant property and various beneficial effects of uric acid mostly in the central nervous system.^{3,22,23} The antioxidant role of uric acid was recently very well established in conditions like ischemic stroke, Alzheimer's disease and Parkinsons disease. Uric acid mainly scavengers the major pathological free radicals like the superoxide anion, peroxy nitrite, hydroxyl radicals, and it also reduces the Fentons reaction thereby reducing the oxidative stress to the neuronal tissues and producing the neuroprotective effect, it was also postulated that uric acid stabilizes the vascular endothelium and since it is a hydrophobic molecule its action was mainly restricted to the extracellular space.²⁴

The role of uric acid in acute ischemic stroke was being evaluated extensively. The long-standing understanding was that uric acid is proatherogenic and increases the risk, and mortality in ischemic stroke but in recent days various other beneficial effects of the stroke were identified. The most important among them is the antioxidant property.

The uric acid was a powerful antioxidant, thereby it scavengers the free radicles in the brain and hence preventing the free radicle injury to the brain.^{3,22} Various studies have shown that increased uric acid levels were associated with a better clinical outcome and reduced severity.^{25,26} Supporting these many studies have proved

the administration of uric acid along with thrombolysis or mechanical thrombectomy had a favorable clinical outcome, better recanalization, and reduced mortality that to preferentially in women and in patients with hyperglycemia.^{26,27} URICO-ICTUS trial also showed that the administration of uric acid in acute ischemic stroke along with thrombolysis had resulted in a reduced ischemic worsening in a group of 262 patients.²⁸

The therapeutic effect of uric acid

Uric acid is a potent antioxidant it acts mainly in the vascular endothelium thereby producing its effects, Yu et al, described the effect of uric acid in hippocampal cells of rats in there is a reduction in cell death in ischemic cells which first showed the beneficial effect of uric acid in ischemic stroke. This was further supported by Haberman et al, showing an improved clinical outcome, smaller infarct in rats with ischemic stroke involving the middle cerebral artery which was treated with uric acid.²⁹

Following various animal studies Chamorro et al, from Spain in a study conducted with 881 patients with an acute ischemic stroke there was a positive correlation showing a 12% increase in clinical outcome following each mg of elevation of uric acid, this effect was contributed to the antioxidant property of uric acid.²⁵ This was further expanded to an extent Phase 2 URICO-ICTUS trial showed that an Intravenous administration of uric acid in acute ischemic stroke patients who were treated with intravenous thrombolysis showed a 6% increase in the clinical outcome than compared with the control.^{26,30} This improved clinical outcome in acute ischemic stroke with uric acid was seen more in females than compared with males and similar outcomes were also seen in hyperglycemic individuals.²⁷

DISCUSSION

The incidence and the prevalence of the stroke is on the rise worldwide with maximum predominance in developing countries like India. The estimated incidence of acute ischemic stroke in Tamilnadu was 119-145/100,000 based on the recent population based studies. And also acute ischemic stroke accounts for a major percentage of morbidity and mortality. Hence, authors are analysing the prognostic significance of uric acid in acute ischemic stroke patients.

From authors review various studies showed that, patients with higher uric acid has a less severe stroke on admission and also less hospital admission days and faced less complications when compared to the patients with lower uric acid group, this was attributed to the anti-oxidant property of uric acid. Due to the postulated antioxidant property of uric acid nowadays various studies were using Uric acid along with Thrombolytic agent for reducing the ischemic damage and reducing the neuron loss.

In a study conducted by Mapoure et al, was 7.10 ± 2.56 .³¹ The mean serum uric acid levels was comparatively on the lower range when compared to other study, this lower range in this study population can be attributed to the exclusion of most of the causes of hyperuricemia in the study population. And also the mean uric acid levels were comparatively higher in males than females, this difference can be due to the effect of oestrogen in uric acid which is still to be proved by further studies.

The correlation of serum uric acid levels regarding the prognostic significance in acute ischemic stroke patients was a wide controversy. Chronic hyperuricemia is atherogenic and it had a negative impact on outcome in stroke, but in acute setting recent days various papers had been published about the beneficial effect of uric acid due to its antioxidant property. This was further supported by the co administration of Intravenous uric acid along with thrombolysis for acute ischemic stroke. Hence, it was concluded that, uric acid had a beneficial effect in a setting of acute ischemic stroke.

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