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POSSIBLE ROLE OF ANTIOXIDANT IN THE MANAGEMENT OF ACUTE ISCHEMIC STROKE: A REVIEW OF THE LITERATURE

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ABSTRACT

Cerebrovascular disease or stroke is a major cause of morbidity and mortality all over the world. It is ably described with the initials 6:6:6, meaning: 6 million people die every year from a stroke, every 6 seconds someone somewhere dies from stroke, and 1: 6 persons worldwide will have a stroke in their lifetime. each year, about 15 million people around the world experience a stroke; of these, 6 million die and 5 million are left permanently disabled. In general, stroke is a disease of the elderly, and so these trends will increase over the next several decades as a result of an aging population combined with the disturbing persistence of many well understood 'modifiable' risk factors, including hypertension, dyslipidemia, cigarette smoking, diabetes, obesity, physical inactivity, excessive alcohol intake and diets high in saturated fats and low in fruits and vegetables. The health burden of stroke is staggering, as loss of a productive life inflicts a heavy toll on patients, families and the society. Yet, this disease has no effective therapeutic treatment beyond a limited (about 2%) treatment with thrombolytics that has a significant adverse effect. In addition, thrombolytic therapy in our resource limited environment purses a serious challenge to neurological practice. A wide variety of currently unproven acute stroke therapies continue to be used around the world. There are significant differences in attitudes of both treating specialists and primary care doctors in different countries. For example, while Traditional medicines are popular in China, in Nigeria Antioxidants are often used. This review tends to focus on the role of Antioxidants (Beta-carotene, Vitamin A, Vitamin C, and Vitamin E) in the management of acute ischemic stroke hoping that, the review would not only create more awareness on stroke management but would inform policy-makers on the urgency and mechanism required for cheap and affordable treatment of acute stroke in resource limited countries like Nigeria. It would also be a useful resource material for

regional, national and international bodies that are involved in the management of patients with acute ischemic stroke, especially in developing nations.

KEYWORDS: Antioxidant, Acute Ischemic stroke, Oxidative stress, Vitamins Cerebrovascular disease.

INTRODUCTION

Although many definitions of stroke exist, the most fitting one for this write up, is that which defined stroke as 'Global or focal disturbance of cerebral function resulting only from a vascular cause with dysfunction lasting more than 24 hours or resulting in death'.[1] The theoretical background for this review is provided by mechanisms of acute ischeamic stroke. Ischemic stroke can be due to local vascular occlusion (thrombus), occlusion from intravascular material that originates elsewhere (embolism), or poor perfusion through a site of pre-existing stenosis. A pre-existing stenosis in the internal carotid artery can lead to a watershed infarction in the zones between the anterior, middle, and posterior cerebral arteries if there is a sudden profound reduction in blood pressure (e.g. cardiac arrest, surgery with hypotension). The aetiology of stroke depends on the age of the patient with atherosclerosis playing a more prominent role in those older than 55years of age. Younger patients are more likely to have arterial dissection, right-left shunting, or coagulopathies associated with their stroke.[1]

Pathogenesis: Normal adult brain cerebral blood flow is 50ml/100g/minute to 60ml/100g/minute, when cerebral blood flow falls below 18ml/100g/minute in baboons, sensory evoked potentials disappear. It was also shown that, when cerebral blood flow fell below 12ml/100g/minute, infarction occurred. Therefore, cerebral blood flow between 10ml/100g/minute and 20ml/100g/minute is considered consistent with ischemic penumbra. Cerebral blood flow below 10ml/100g/minute is considered compatible with infarction. These delineations are not absolute because time is also a factor in the fate of tissues.[1] An ischemic stroke results when cerebral blood flow to an area of the brain is interrupted, leading to ischemia. The resultant ischemia produces impaired energy metabolism and depolarization of cells, which leads to an accumulation of calcium ions in the intracellular space, elevated lactate levels, acidosis, and production of free radicals. A free radical is any atom, group of atoms or molecule with an unpaired electron in its outermost orbital. Free radicals are produced in small quantities by normal cellular processes in all aerobic cells and they are inherently toxic; they can react with and damage proteins, nucleic acids, lipids and other

classes of molecules such as the extracellular matrix glycosaminoglycans (e.g. hyaluronic acid). The sulphur-containing amino acids and the polyunsaturated fatty acids (found in high concentrations in the brain) are particularly vulnerable.

Fortunately, cells possess appropriate defense mechanisms in the form of free radical scavengers and enzymes which metabolize free radicals or their precursors.[2,3] This free radical scavengers and enzymes are generally referred to as antioxidants. Generally, antioxidants are classified into; primary, secondary and tertiary antioxidants. Primary antioxidant are basically consigned with prevention of oxidant species, secondary antioxidants on the other hand, sub-serve the function of clearing Reactive Oxygen Species (ROS) as scavengers, while tertiary antioxidants are dietary antioxidants that repair oxidants.

During severe brain ischaemia, insufficient oxygen is available to accept electrons passed along the mitochondrial electron transport chain, leading to eventual reduction (‘electron saturation’) of the components of this system. The free radicals which are elevated in cerebral ischaemia include O2 –, hydroxyl (OH) and nitric oxide (NO). Nitric oxide is generated primarily by neuronal and inducible NO synthases (NOS). Like other free radicals, the free radicals which are elevated in cerebral ischaemia react with and damage proteins, nucleic acids and lipids, particularly the fatty acid component of membrane phospholipids, producing changes in the fluidity and permeability of the cellular membranes (lipid peroxidation).[2] The free radicals also cause microvascular dysfunction and disrupt the blood–brain barrier, leading to brain oedema. In addition, the conversion of xanthine dehydrogenase to xanthine oxidase promotes the cellular formation of toxic oxygen free radicals such as the superoxide anion, which further breaks down membrane cytoskeletal and nuclear structures.

Oxidative stress: Oxidative stress is a widely recognized but poorly understood component in stroke. Growing evidence indicates that oxygen radicals can produce remarkably specific actions in signaling cascades that can initiate apoptosis.[5] In addition, oxygen radicals exert an important role in promoting thrombosis and permeability increases in the vasculature that can greatly complicate the final outcome from stroke.[6] Molecular oxygen is capable of oxidizing any biological molecule and routinely does so as the terminal electron acceptor in normal metabolism.[7] Molecular oxygen has a most unusual bonding arrangement, with two unpaired electrons occupying separate orbitals. In essence, this small molecule preferentially exists as two free radicals rather than having all of the electrons paired. Consequently, oxygen can accept only one electron sequentially from biological molecules at a time. This

prevents oxygen from rapidly oxidizing most biological materials because they have filled orbitals containing two electrons of opposite spin and giving up only one electron is energetically highly unfavorable. Oxygen can be reduced by a variety of enzymes in the body, including reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and xanthine oxidase, to produce free radicals. The addition of one electron to molecular oxygen produces superoxide anion.[7]

Negative effect of oxygen radical among patients with acute ischemic stroke: Oxidative stress is generally bad because it amplifies tissue injury. However, there has also been strong evolutionary pressure for cells to produce oxygen radicals as antimicrobial defenses. Because these molecules are generally reactive, they are produced by a variety of inflammatory cells including neutrophils and macrophages to injure or kill invading microorganisms and parasites. Therefore, Oxygen radicals can clearly amplify the injury produced by cerebral ischemia.

An important source of Oxygen radicals implicated in oxidative stress-mediated brain damage is the oxidant reactions due to the formation of peroxynitrite, a powerful oxidant that results from the interaction between NO and superoxide. This anion has been shown to cause cell damage by several mechanisms that include lipid peroxidation, tyrosine nitration, sulphydryl oxidation, nitrosylation, and DNA breakage.[1] Neurones undergoing oxidative stress related injuries typically display a biphasic or sustained pattern of extracellular signal regulated protein kinase (ERK1/2) activation. With reperfusion, reactive oxygen radicals may be generated as by-products of the reactions of free arachidonic acid (released from membrane phospholipids during ischaemia) to produce prostaglandins and leukotrienes, which perhaps lead to reperfusion injury to the brain and its microvessels. Additionally, one can consider peroxynitrite to be a binary weapon assembled from two less reactive intermediates. Peroxynitrite anion has a pKa of 6.8, allowing a substantial fraction to be protonated at neutral pH. The resulting peroxynitrous acid is far more reactive, with 30% decomposing to form hydroxyl radical and nitrogen dioxide (NO2).[6] Furthermore, activation of the N-methyl-D-aspartate receptor by an increase in glutamate leads to a cascade of chemical reactions, which ultimately lead to cell death ("theory of excitotoxicity"). Modulators of this receptor include polyamines, glycine, magnesium and zinc.

Current organization of stroke services: The organization of acute ischemic stroke care varies, on one extreme, from the virtually total lack of resources in rural Africa, to helicopter

transport and coordinated high-technology care in developed societies. Stroke is an emergency therefore patients with stroke should be urgently admitted to hospital to ensure accurate diagnosis, determination of likely pathogenesis and secondary prevention, enable coordinated acute medical care, and ensure appropriate rehabilitation.[8] In recent years, there are three major evidence-based advances in acute stroke therapy that includes: (1) the proven benefits of organised care in stroke units,[9,10] (2) thrombolysis using intravenous tissue plasminogen activator (tPA) within 3 hours of stroke onset, (3) a modest reduction in adverse outcomes achieved with aspirin used in the first 48 hours after stroke onset.[11,12]

Despite the current revolution in the management of acute stroke, there is still a widespread perception of therapeutic nihilism and inadequate organization of stroke care in many countries. There is a vast gulf in care standards between stroke patients in affluent, well-resourced countries and those in developing nations. Even in industrialized countries, cost constraints and changes in health care systems are likely to affect acute stroke services. Results of clinical trials are producing an impetus to change the clinical management of stroke. These evidence-based results will emphasize deficiencies in the ability of health organizations in different countries to deliver these new treatments. There will be increased emphasis on showing not only efficacy but also cost-effectiveness of new acute therapies. Increasingly, neurologists and other physicians with an interest in stroke are becoming involved in public education and policy formulation concerning stroke management.

Antioxidants: The oxidative modification hypothesis of atherosclerosis is that oxidation of low-density lipoprotein cholesterol (lipid peroxidation) allows it to accumulate in artery walls and promote atherosclerosis. This has prompted several studies of the effect of reducing oxidative stress by means of antioxidants. Antioxidants vitamins may be inform of non-enzymatic antioxidants such as: uric acids, organosulfur compounds, minerals, vitamins A, ascorbic acid, E and K, enzyme cofactors, peptides and polypeptides.

Vitamin C: Vitamin C is a water-soluble antioxidant in plasma that helps regenerate oxidized vitamin E. Large observational epidemiological studies suggest that increasing plasma vitamin C concentrations are associated with a reduced risk of stroke.[5-7] A population-based prospective study of 20649 British men and women aged 40 to 79years without prevalent stroke who were assessed during 1993 to 1997 and followed up for average of 9.5 years for the occurrence of incident stroke showed that persons in the top quartiles of baseline plasma vitamin C concentration had a 42% lower risk (relative risk, 0.58; 95% CI,

0.43–0.78) than did those in the bottom quartile independently of age, sex, smoking, body mass index, systolic blood pressure, cholesterol, physical activity, prevalence of diabetes and myocardial infarction, social class, alcohol consumption. More recent supportive evidence comes from a large observational study of 23119 Japanese men and 35611 women aged 40 to 79years without a history of cardiovascular disease who were followed for a median period of 16.5years for the occurrence of stroke. The multi variable hazard ratio for the highest versus lowest quintile of vitamin C intake was 0.70 (95% CI, 0.54–0.92) for total stroke.[6,7] Three large RCTs, which minimize bias and confounding, have shown no effect of vitamin C on stroke risk.[6-9] The Heart Protection Study randomly assigned 20536adults with prior stroke, coronary disease, other occlusive arterial disease, or diabetes to receive antioxidant vitamin supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily) or matching placebo.[11] After 5 years, the plasma concentration of vitamin C increased by one third among those assigned vitamins but there was no significant difference in stroke (5.0% vitamins versus 5.0% placebo) or any major vascular events (22.5% versus 22.5%; rate ratio, 1.00, 95% CI, 0.94–1.06).[9]

Vitamin E: Vitamin E is a lipid-soluble antioxidant which increases resistance of low-density lipoprotein cholesterol to oxidation, reduces smooth muscle cell proliferation, and reduces adhesiveness of platelets to collagen. It inhibits lipid peroxidation by scavenging reactive oxygen species and preserving cell membranes.[12-14] A systematic review of RCTs investigating the effect of vitamin E on stroke with 1 years of follow-up and published before January 2010 included 9 trials in which a total of 118765 participants were randomized to vitamin E(n59357) or placebo (n59408). Among the 7 trials that reported data for total stroke, vitamin E had no effect on the risk of incident total stroke compared with placebo (RR,0.98;95% CI, 0.91–1.05).[15] However, among the 5 trials that reported hemorrhagic and ischemic stroke, vitamin E was associated with an increased risk of incident hemorrhagic stroke (0.44% vitamin E versus 0.36% placebo; RR, 1.22;95% CI,1.00–1.48; P0.045) and a reduced risk of ischemic stroke (1.94% vitamin E versus 2.16% placebo; RR, 0.90;95% CI, 0.82–0.99; P0.02).[11] A subsequent meta-analysis of 13 RCTs of vitamin E in 166282 participants showed no significant benefit of vitamin E in the prevention of stroke of any type (RR, 1.01; 95% CI,0.96–1.07; Table 1), ischemic stroke (RR, 1.01. 95% CI, 0.94–1.09), or hemorrhagic stroke (RR, 1.12; 95% CI, 0.94–1.33).[16]

Vitamin A and Beta-Carotene: Beta-carotene is a fat-soluble antioxidant and the biologically active metabolite of vitamin A.[5,6] Vitamin A has beneficial antioxidant effect by combining with peroxyl radicals and neutralize their damaging effect.[13] However, A meta-analysis of 3 randomized controlled trials (RCTs) of beta-carotene in a total of 82 483 participants showed no effect of beta-carotene on the rate of stroke compared with control (OR, 1.0; 95% CI, 0.91–1.09; P0.92).[5] Moreover, beta-carotene was associated with an increased risk of cardiovascular mortality (OR, 1.10; 95% CI, 1.03– 1.17; P0.003) and all-cause mortality (OR, 1.07; 95% CI, 1.02–1.11; P0.003).[17]

Other vitamins: B Vitamins Folic Acid and Vitamin B12Randomized trials indicate that folic acid supplement at ion lowers plasma total homocysteine concentrations (tHcy) by approximately 25% (95% CI, 23%–28%) and vitamin B12supplementation lowers tHcy by approximately 7% (95% CI, 3%–10%).17 Lowering tHcy is associated with a lower risk of total stroke and lower risk of ischemic stroke due to large artery disease, small artery disease, and embolism from the heart, independent of other factors.[18-21]

CONCLUSION

Oxidative stress is a widely recognized but poorly understood component in stroke. Growing evidence indicates that oxygen radicals can produce remarkably specific actions in signaling cascades that can initiate apoptosis. Furthermore, oxygen radicals exert an important role in promoting thrombosis and permeability increases in the vasculature that can greatly complicate the final outcome from stroke. Fortunately, cells possess appropriate defense mechanisms in the form of free radical scavengers and enzymes which metabolize free radicals or their precursors (antioxidants).[22-24] Generally, use of vitamins as antioxidant is promising area of research to prevent CVD. It has been reported that, antioxidant vitamins have ability to prevent the oxidation of low density lipoprotein such as cholesterol that is common cause of CVD. Additionally, vitamin E prevents coronary heart disease.[25] While Coenzyme Q10 play the role of electron transport chain processes, scavenges lipid peroxyl species and minimizes their effect after their formation.[26]

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