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Potential Biomarkers in Stroke and Current Therapeutics

Atiksha Rawat*

Division of Pharmaceutical sciences, Shri Guru Ram Rai Institute of Technology and Sciences, Patel Nagar, Dehradun, Uttarakhand, India

*Address for Correspondence:** Atiksha Rawat, Division of Pharmaceutical sciences, Shri Guru Ram Rai Institute of Technology and Sciences, Patel Nagar, Dehradun, Uttarakhand, India

ABSTRACT- Stroke is a brain injury where a sudden interruption of the blood supply in brain part and the brain does not receive the enough blood flow due to which there is a lack of oxygen and glucose and without blood supply the brain cells begin to die (cerebral infarction) and cause brain damage. So there is a need to understand the pathophysiology and to effective biomarkers in acute ischemic stroke and may help to enhance the current clinical outcome of stroke. Various biomarkers are associated with the pathophysiologic mechanism and they may help in stroke assessment, diagnosis, prognosis or treatment. There is a higher rate of morbidity and mortality in stroke. Hence a better pharmacological management is desired for the fast recovery and treatment from stroke. Thrombolytics, antihypertensive, anti-platelet therapy, antioxidants, rehabilitation technique and their combinations e.g. Aspirin and clopidogrel, Aspirin and dipyridamole, ramipril and telmisartan, IgG- glial cell-lined derived neurotropic factor (GDNF) and IgG – tumor necrosis factor receptor(TNFR) etc. and various surgical treatment such as carotid endarterectomy, stereotactic radiosurgery, hypothermia, revascularization of the blood supply, endovascular treatment of aneurysms and angioplasty and stenting of vessels in the neck and brain are also required for the beneficial outcomes in future.

Key-Words: Stroke, Biomarker, Pathophysiology, Combinational therapy, Surgical treatment

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INTRODUCTION

Stroke is a neurological disease which cause of disability and death [1]. The blood supply of brain in stroke is obstructed because of ischemia and hemorrhage which causes the brain dysfunctioning. Ischemia caused by blockage in blood vessels via thrombosis and arterial embolism vasoconstriction. In ischemia reduction in sufficient blood flow to alter the normal cellular function [2].

Stroke has two major categories of brain ischemia one is global-ischemia and other one is focal ischemia. In focal ischemia models, the middle cerebral artery is occluded, either temporarily (vessels are blocked up to 3 hrs) or permanently (vessels) are blocked usually for one or more days) to allow the reperfusion [3-4].

There are two types of risk factors for causing stroke one is controllable risk factor includes high cholesterol, smoking tobacco use, hypertension, diabetes, obesity blood disorder and certain drugs (i.e., anticoagulant and birth control pills). Rather than this uncontrollable risk factors include age, gender, family history, transient ischemic attack (TIA) artery abnormalities, fibro muscular dysplasia [5-6]. So there are some treatments available for stroke. Only tissue plasminogen activator (tPA) as a drug for stroke treatment approved by FDA which reopens the blocked blood vessels [7]. Recovery and prevention of stroke a good pharmacological management is required for better treatment which can reduce the risk factors of recurrent stroke.

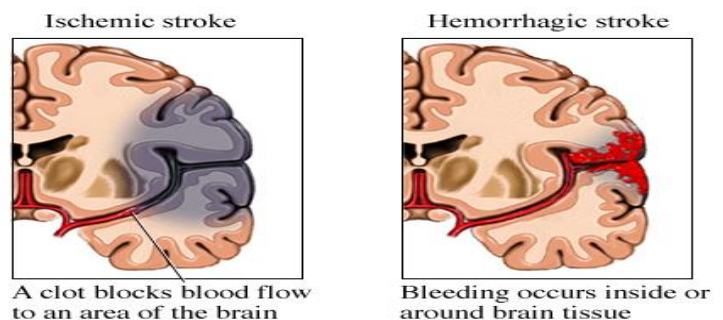| Access this article online	
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Fig. 1: Types of stroke [3]

Mechanism of Ischemic Stroke

Ischemic cerebrovascular disease is caused by embolism, thrombosis and focal hypoperfusion, which leads to an interruption or reduction in cerebral blood flow (CBF) affect the neurological function [8]. In adult the normal range of CBF is 50-55ml/100g/min, the brain damage is reversible and brain infarction occurs [9]. The pathophysiology of stroke is complex and involves various processes, including energy failure, oxidative stress, excitotoxicity, oxidative stress, inflammation distruption of the blood brain barrier (BBB), apoptosis, adhesion molecules, activation of glial cells and infiltration of leukocytes.
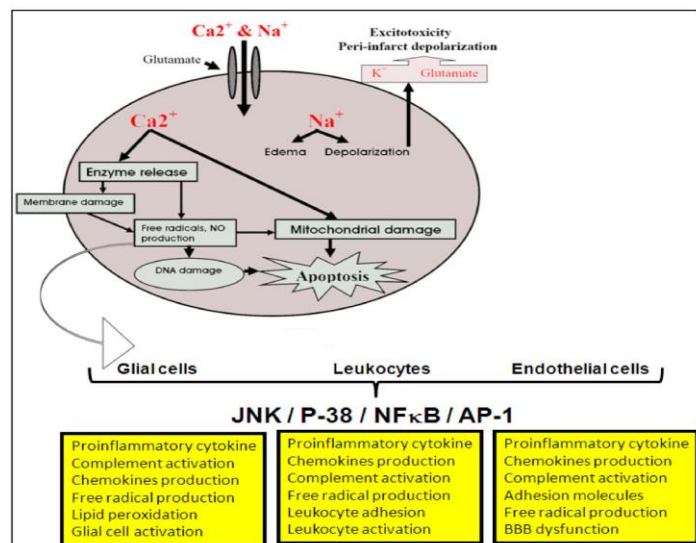

Fig. 2: Major cellular patho-physiological mechanism of ischemic stroke [4]

Excitotoxicity

Excitotoxicity defines to sequences of events which are induced by excessive accumulation of excitatory amino acids which leads to toxic increases in intracellular calcium ions [10]. After reduction or termination of CBF and energy dependent Na^+-k^+-ATP enzyme fail due to reduced in glucose dependent ATP generation, resulting in the flow of various ions into the cell, including Na^+, Cl^-, Ca^{2+} and these ions can interrupted by the overstimulation of 1-amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-d-aspartic acid (NMDA) and kinate – glutamate type receptors, glutamate as major excitatory neurotransmitter in brain, deposite in the extracellular space in ischemia and activate its receptor and after activation produces alteration in the intracellular ion concentration including most calcium and sodium ions. These cells become depolarized, which cause more Ca^{2+} influx and more glutamate release may result that acute swelling of cells which ultimately causing cell death. Calcium as a secondary messenger activates multiple signaling pathways that lead to necrosis or apoptosis.

Oxidative Stress

Neurons are mainly exposed to a base line level of oxidative stress that includes exogenous and endogeneous

sources, as are all in body cells. Oxidative stress occurs when there is imbalance between production of free radicals and endogeneous scavenging capacity of cellular antioxidants [11-12]. Free radicals are those molecules with one or more unpaired electrons and highly reactive which can react with DNA, lipids and proteins that cause dysfunction and damage. In stroke induced brain injury, include superoxide anion (O_2), hydroxyl radical (OH·), nitric oxide (NO) and hydrogen peroxide (H_2O_2). O_2 is generated earliest, while OH· is the most toxic. In ischemic stroke, superoxide anion initially generated radical through various ways, including mitochondrial electron transport process [13], xanthine oxidase (XO) process which is to be a major source for the generation of oxygen free radicals in ischemia and reperfusion [14,15] and metabolism of arachidonic acid (AA) by the cyclooxygenase (COX) pathways. H_2O_2 is formed by superoxide anion and it is the sources of (OH·). NO is released from L-arginine by nitric oxide synthases (NOS) which are calcium dependent. NO can react with superoxide anion to produce peroxynitrite (ONOO), and another highly toxic oxygen species [16]. On the another hand, antioxidants like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) degrade superoxide anion into H_2O_2, additionally transfer H_2O_2 into H_2O. Additionally to these defenses, the brain is vulnerable to oxidative stress resulting from ischemia and reperfusion.

Increase calcium influx which disrupts mitochondrial integrity from which Cytochrome C is released to trigger apoptosis that cause varying degrees of damage, ultimately cause cell death [17].
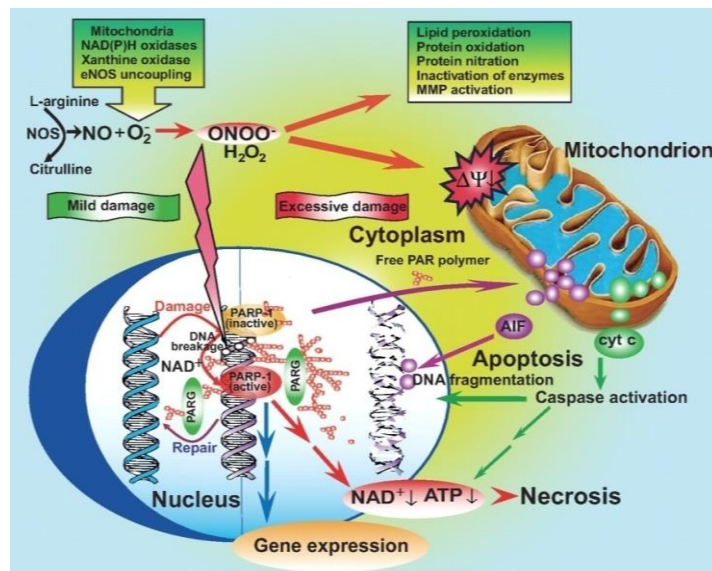

Fig. 3: Necrosis occurring due to oxidative stress at cellular level (4)

Inflammation

Various cell types contribute to post-ischemic inflammation, including endothelial cells, microglia and neurons and astrocytes [18]. The major elements in an inflammation reaction involve signaling molecules, inflammatory cells, adhesion molecules and transcriptional

regulators. Reperfusion occur and upregulated adhesion molecule which cause release of cytokines to cause inflammation which leads to release of free radicals like ROS and cause death. Oxygen free radical, increasing amount of calcium and ischemia itself can activate astrocytes and microglia to produce pro-inflammatory cytokines like tumor necrosis factor-1(TNF-α), interleukin-1 (1L-1) and interleukin- 1β (1L-1β) as well as Neuroprotective factors, such erythropoietin, metallothionein-2 and TGFb1 [19]. Most of these cytokines can induce the production of some adhesion molecules such as selectins such as (E-selectins, P-selectins), immunoglobulin superfamily (intercellular adhesion molecule-1, vascular endothelial adhesion molecule-1) and integrins. Meanwhile interleukin-8 (1L-8), monocyte adhesion protein chemistry -1(MCP-1) and other chemokines plays a very important role in the migration of inflammatory cells. By the help of matrix metalloproteinase (MMP), the extracellular matrix is broken down and inflammatory cells infiltrate the brain parenchyma. After 4-6 hr onset of ischemia circulating leukocytes reach the penumbra.

The inflammatory injury is induced by various molecules such as cell adhesion molecules (integrins, selectins and immunoglobulins), chemokines (CINC, MCP-1) cytokines (IL-1, IL-6, TNF-α, TNF-β), Inducible neuronal nitric oxide synthase (iNOS) which produced by endothelial cells, microglial cells, leukocytes and activated asrtocytes and these all are contributed to the irreversible damage.

The assignment of neutrophils to ischemic brain begins with rolling of neutrophil on activated endothelial blood vessels walls then mediated by selectins and followed by neutrophil adherence and activation which mediate by integrins and immunoglobulins and when neutrophils immigrate into the cerebral parenchyma, that causes blood brain barrier BBB disruption.

After reperfusion the assignment of neutrophils can prevent complete restoration of cerebral blood flow and obstruct the microcirculation. If once neutrophils penetrate into the ischemic brain they release of free radicals and proteolytic enzymes which cause tissue damage.

Chemokines and cytokines are also contributed to brain injury. In cerebral endothelia cells both il-1 and TNF-α induces adhesion molecule expression and initiate the accumulation of neutrophils and transmigration. In addition TNF-α disrupts the BBB blood brain barrier, stimulates the production of acute-phase protein and also stimulates the induction of other inflammatory mediators while TNF-β plays an important role in neuroprotective in pathogenesis of stroke. Neutrophills are the first leukocyte subtype involved in inflammation [20].

Blood Brain Barrier (BBB) Dysfunction

Disruption of blood brain barrier in acute ischemic stroke varies considerably from 15 - 66% [21]. The major reasons that contribute to the damage of the BBB in acute ischemia and reperfusion injury are free radicals and inflammation. Matrix metalloproteinase MMPs and serine proteases are essential breakdown of the extracellular matrix around cerebral blood vessels and neurons, and there action leads to the disruption of BBB, brain edema, hemorrhage, and cell death. Therefore MMPs are thought to be direct factors which lead to brain damage [22]. BBB damage mentioned to be a biphasic in ischemic stroke [23].

After 2 hr ischemia onset, BBB gets a transient opening that may results from oxidative stress which trigger activation of MMP-9 [24] and MMP-2 [25].

Apoptosis

There are two forms of cell death, necrosis and apoptosis. Many brain cells in ischemic injury undergo apoptosis, which in contrast to necrosis which is a relatively orderly process that allows cell to die with minimal damage and distruption to neighboring cells [26]. There is minor inflammation or release of genetic material [27]. They are potentially recoverable for some time after the onset of stroke. For activation of apoptosis caspase-dependent is an important mechanism. It includes the intrinsic pathway, which is initiated by release of cytochrome C by mitochondria and resulted in activating caspase -3 and the extrinsic pathway which triggered by activation of cell surface death receptors and resulting in caspase-8 [28].

Biomarkers in Acute Ischemic Stroke

During ischemic stroke, ideal biomarkers should possess characteristics that include sufficient selectivity, reactive, predictable clearance, stable and primarily release shortly after infarction, potential for risk assessment and guidance therapies, and ability to be quantitatively and rapidly measured by cost effective methodologies [29]. Various novel biomarkers of cerebral injury which is related to the pathophysiology reviewed above, and in clinical scenarios, they may have applications in stroke prediction, assessment, diagnosis, prognosis or treatment.

Coagulation/thrombosis biomarkers

In mostly cases, the main cause of acute ischemic stroke is atherothrombosis of large cervical or intracranial arteries, or embolism from heart or cerebropetal arteries [30]. In this condition, molecules involved in coagulation or thrombosis are associated with ischemic stroke, including fibrinogen, von Willebrand factor (vWF), which is reported in recent years. In prediction value, fibrinogen was reported by Fibrinogen Studies Collaboration that plasma fibrinogen level was significantly related with coronary heart diseases(CHD), stroke and other causes of vascular and non vascular mortality [31], and by community- based study in Taiwan which is 72% increase(hazard ratio, 1.72; 1.02 to 2.90) in ischemic stroke that was observed for individuals with fibrinogen ≥8.79μmol/L compared with those <7.03μmol/L, suggested fibrinogen is independently predicted future ischemic risk [32]. And also D-dimer and vWF are reported to be related with increased risk of stroke in older men, and these associations were independent of inflammation for D-dimer, this is a significant predictor of stroke in hypertensive men[33]. Laskowitz et al [34] reported a five panel biomarkers (S100B, vWF, B-type NGF, MMP9 and MCP-1) can diagnose the stroke with 93% specificity

and 92% sensitivity. D- dimer is to distinguish cardioembolic stroke from some other subtypes of ischemic stroke[35]. Combined of D-dimer with D-dimer/fibrinogen ratio, CRP and erythrocyte sedimentation and it can be separate large vessel from cardioembolic stroke [36]. So it is reported that plasma D-dimer level on admission is significantly associated to infarction volume and functional outcome in cardioembolic stroke in non-valvular arterial fibrillation patients [37].

Biomarkers in Oxidative Stress

Science direct measurement of reactive oxygen species (ROS) in brain is difficult in humans because of their endogenous antioxidants, transient nature and limitation of measurement as well as several biological substances whose chemical structure has been modified by free radicals have been investigated as potential indirect biomarkers in oxidative stress.

Endogenous Antioxidants

Endogenous antioxidants have enzymatic (CAT, GPX and SOD) and non enzymatic antioxidants (retinol, uric acid, ascorbic acid, caroteniod and tocopherol) which consists of the cellular protective antiradical mechanism.

Antioxidants catalase (CAT) and glutathione peroxidase (GPX) in a safe way can dispose H_2O_2 to protect neural cells from oxidative stress. In ischemic patients clinical researchers showed that CAT and GPX activity were significantly higher as compared to controls [38-39] and CAT can be considered as adequate marker for positive outcome [39]. And on the other hand, GPX activity found to be significantly lower in ischemic patients compared with controls [40, 41]. So this debate may result by the degree of damage by ROS, since antioxidant enzymes might be induced by oxidative stress and their activity/level may increase or else consumed (thus decreasing their levels and activity [42].

In stroke, SOD is the most studied antioxidant enzyme whose changes of activity/concentration in blood were also extremely disputed. Studies have found that the SOD activity in patient's plasma [39-40], serum [43] and red blood cells [41] to be significantly lower than control group, while other found that the SOD activity in red blood cells have a contrary result [44]. Similarly, in ischemic patients blood concentration of SOD is controversial. So, this debate may because the three different isoforms of superoxide dismutase (CuZnSOD, MnSOD and EC-SOD), and the different analysis methods [40], so most of the studies suggested that the SOD levels and concentration has a significant correlation with infarct size and neurological deficit.

Biomarkers of Oxidative Product

DNA, proteins and lipids can be damage by ROS and many metabolites produced during this process can be measured in the serum.

Biomarkers of lipid peroxidation

The brain cellular membrane lipids extremly rich in rich in polyunsaturated fatty acid side chains and this is highly prone to free radical attack that results in lipid peroxidation include biomarkers such as thiobarbituric acid-reactive substances (TBARs), malondialdehyde (MDA), lipid peroxides (ROOH) and F2-isoprostanes(F2IPs). The plasma concentration of TBARs, MDA and lipid peroxidaton are mostly used biomarkers of oxidative stress. In cerebral ischemia patients many studies demonstrated that concentration of TBARs and MDA are higher than in controls, and they are correlated with infarct size, patient's and clinical stroke severity [38,45-46]. However, insufficient specificity of both MDA and TBARs for measurement of lipid perpxidation, because MDA can present from both lipid peroxidation products and also from endoperoxides degradation [42], and when reacting with TBA, other molecules can depletes MDA which increases the amount of MDA to react with TBA [47].

Prostaglandin–like products (F2IPs) of non-cyclooxygenase free radical induced peroxidation of arachidonic acid and because of its good stability, sensitivity and specificity they are reliable marker. They can be detecting in plasma and urine [ ]. Kelly et al. reported that the plasma concentration of F2IPs were increased primarly in ischemic stroke patients as compared to control [48].

Biomarkers of DNA oxidation

The product of DNA oxidation is 8-hydroxy-2'-deoxyguanosine (8-OHdG) has been mostly used as excellent biomarkers of oxidative stress [49]. An animal study established that the plasma concentration of 8-OHdG were increased and significantly related to brain content of 8-OHdG[50]. In patients with high risk of vascular recurrence or vascular death it could be useful to identify and to determine some particular atherosclerotic plaques characterstics [51].

Biomarkers of protein oxidation

In humans there is an in sufficient studies in protein oxidation biomarker, however, a study on patients with Alzheimer's diseases and vascular dementia has established that estimation the protein carbonyl and the dityrosin contents of immunoglobulin G (IgG) can be executable not only for its delicate to dietary antioxidant supplementation and a associated long –half-life of 15 days that make IgG a satisfactory marker of oxidative stress [52].

Biomarkers of inflammation

Serum level of IL-1β, IL-6, IL-8, IL-17, TGF-β, ICAM-1, VCAM1, P-selectin, E-selectin, L- selectin, MCP-1 and TNF-α has shown ascent, compared to controls [53]. In ischemic stroke patients, the serum concentration of IL-6, VCAM-1, BDNF, IL-1β, TNF-α, ICAM-1 and MMP-2/9 were found significantly different when compared to other neurological diseases and many of them are correlated with

infarct size and neurological deficit such as MMP-2/9, BDNF, TNF-α, ICAM-1 [54].

In inflammatory reaction, TNF-α is a major cytokine with a myriad of effects [55] reported that inhibition of production of MMPs by TNF-α and also reduce the brain edema in ischemia. While on contrary others shown that TNF-α activated the production of MMPs and increases the inflammatory injury [56]. Different results conclude a complex role of TNF-α in inflammatory mechanisms.

C-reactive protein (CRP) as an important indicator of inflammation has been studied extensively. In ischemic stroke patients increased the concentration of high sensitivity C-reactive protein (hsCRP) has been observed [57]. CRP concentration is correlated with infarct size volume and neurological deficit in ischemic stroke, and has a potential prognostic value for poor outcome [58].

Management of Ischemic Stroke

The central goal of therapy in acute ischemic stroke is to preserve tissue in the ischemic penumbra, where perfusion is decreased but enough to stave off infarction. Administration of intravenous (IV) recombinant tissue- type plasminogen activator (rt-PA) and intra-arterial approaches, attempt to establish revascularization therefore, penumbra cells can be rescued before irreversible injury occurs. Many surgical and endovascular techniques have been studied in the treatment of acute ischemic stroke [59].

Supplying vessels assessment and brain imagining were required to determine the cause and type of stroke and it may also help to estimation the site and cause of arterial obstruction [60]. Brain ischemia and myocardium are shows common pathological changes therefore, the current therapy are given such as anti-platelet therapy, anticoagulant therapy, thrombolytic therapy, hypercholesterolemia, clot disruption, hypertension treatment therapy, antioxidant therapy and herbal drug therapy. Recovery and prevention of stroke is a good pharmacological management for better treatment which can reduce the risk factor of recurrent stroke. Some surgical techniques are also used to treat ischemic stroke. Different therapies of stroke treatment are illustrated in Table 1.

Thrombolytic therapy

Thrombolytic drugs burst the blood clots or dissolve blood clots and this process known as thrombolysis. It is also known as clot busting [78]. If the patients have acute ischemic stroke, the risk of bleeding can increased and pretreated with antiplatelet or anticoagulant drugs [79]. Thrombolytics drugs dissolve the blood clots by activating the plasminogen which converts into plasmen which is proteolytic enzyme which break or degrade thrombus by breaking fibrinogen, fibrosis monomers and cross-linked fibrin molecules, that is present in thrombus [61].

Table 1: Some combinational therapies of ischemic stroke

Stroke Treatment	Combinational therapies
Thrombolytic therapy	Plasminogen activators e.g- Altepase, Streptokinase, Reteplase, Tenecteplase [61-64]
Antiplatelet therapy	Aspirin, Triflusal, Ticlopidine, Clopidogrel [65-69]
Hypercholesterolemia	Statins [70]
Hypertension treatment	Angiotension type-1 receptor blockers, α-blockers [71]
Antioxidant therapy	Melatonin, Vitamin E, Glutathione, Superoxide dismutase(SOD), Catalase, Tocopherol, Ascorbic acid [70,72-73]
Combinational therapy	(Clopidogrel + aspirin), (Aspirin + dipyridamole), (Telmisartan + ramipril) [74-76]
Rehabilitation	Stroke rehabilitation program, Outpatient rehabilitation for stroke, Muscle relearning [77]
Anticoagulant therapy	Heparin, Warferin [59]
Surgical treatment	Carotid Endarterectomy, Stereotactic Radiosurgery, hypothermia, Endovascular treatment, Revascularization of blood supply [59] etc.

Streptokinase (SK)

It is plasminogen activators which formed the SK/Plasminogen complex. It is CS-hemolytic streptococci group which derived protein that showed significant rates of ischemia and systemic hemorrhage [62].

Because of drug failure or trail design failure, SK (Streptokinase) trials was unsuccessful in stroke but at low dose it was proven that in a properly trail it may have beneficial effects on stroke when other alternative will not present [80-81].

Alteplase (Recombinant Human Tissue Type Plasminogen Activator rtPA)

Alteplase is a serine protease. It have plasma half-life of 3.5 min. it maintained the clump penetration because it highly binds with surface fibrin and detention the restoration flow that increases the risk of recurrent of occlusion.

The rtPA have some neurotoxic properties including activation of metalloproteinase that may increase the permeability of Blood- Brain –Barrier which leads to cerebral hemorrhage and edema. rtPA is used in the first line therapy of acute ischemic stroke. rtPA shows beneficial effect if it was administer within 3hr of the initiation of stroke but after 3hr administer of rtPA shows lesser beneficial effects [82].

Antiplatelet therapy

Antiplatelet drugs are those that inhibit the thrombus formation and decreases platelet aggregation in blood.

Aspirin

Aspirin is a non-steroidal anti-inflammatory drug which is cyclo-oxygenase inhibitors. It inhibit the protection of thromboxane, which in normal condition binds platelet molecules with each other and to grow a patch over damaged blood vessels walls. In ischemic stroke patients, low dose of aspirin (50-325 mg/kg) avoid the risk of motion or drift (motility) and ischemic injuries [74] and higher dose of aspirin has some undesirable side effects like gastrointestinal ulcers, tinnitus and stomach bleeding [83].

Triflusal

Triflusal (2-acetoxy-4-trifluoromethylbenzoic acid) is used to decrease the aggregation of platelet in blood. It inhibits COX1 and COX2. The active metabolite (2-hydroxy-4-trifluromethylbenzoic acid) HTB of triflusal hydrolyze immediately when triflusal administer orally and HTB have power to cross the blood brain barrier (BBB) and it has been recently reported in healthy volunteers [84]. It reduces the hemorrhagic complications and is well tolerated as compared to aspirin [66].

Adenosine diphosphate receptor inhibitors
Prasugrel

Prasugrel is a platelet aggregation inhibitor [67]. Recently prasugrel was examined as new P2Y12 antagonist receptor which can be used in the treatment of atherothrombosis in patients. In the case of higher bleeding rates, the clinical benefit of prasugrel was higher than clopidogrel. Prasugrel needs to biologic conversion to active metabolites and shows the therapeutic action because prasugrel is a prodrug. It inhibits the ADP- induced platelet aggregation and produce greater effects than clopidogrel [85].

Ticagrelor

Ticagrelor is an inhibitor of platelet aggregation. It antagonizes the adenosine diphosphate (ADP) P2Y12 receptor on platelet irreversibly. It shows beneficial effects in ischemic stroke patient [86,87]. It shows the platelet reactivity and produce beneficial effects in ischemic stroke [69].

Hypercholesterolemia Treatment

Increases the cholesterol or plaque in the arteries block the normal blood flow to the brain and causes stroke and also the increase risk of heart diseases and atherosclerosis. Current studies demonstrate that the statins as re-educates inhibitors significantly decreases the risk of ischemic stroke. Statins have various mechanisms to decrease the risk of stroke, like degradation of plaque, by enhancing the bioavailability of nitric oxide, by homeostasis and by decreasing the low density lipoprotein cholesterol [70].

Hypertension Treatment

Prevention of secondary stroke, blood pressure control will be required. It can control the hypertension by giving the combination therapy. Recent studies reported that the new hypertensive drugs (angiotensin type-1 receptor blockers, α-blockers, calcium channel blockers) were more effective in the prevention of stroke then older class drugs (diuretics, β- blocker) [71].

Antioxidant therapy

Oxidative stress occurs when an imbalance between the production of free radical and defence power of cell against free radicals in biological system. Increases the production of reactive oxygen species (ROS) after brain injury and it causes cellular damage (i.e. lipids, nucleic acids and proteins) by several molecular pathways which leads to cause cell death [88-89]. So antioxidants are used for preventing or reducing the oxidative stress and reactive oxygen species and it shows beneficial effects in cerebral injury [90-91]. Because of their physical properties such as water solubility (e g. Vitamin C) or lipid solubility (e g. vitamin E) there are several antioxidants, which crosses the BBB blood brain barrier. In the treatment of stroke and stroke related oxidative stress antioxidants shows neuroprotective effect [92].

Superoxide dismutase

They are enzymes which contain antioxidant properties but have undesirable results in experimental stroke models. Therefore, synthetic SOD/catalase, newly reported EUK-134 was examined that shows cytoprotective properties and also shows SOD properties. It shows positive effect in the stroke patients when it significantly decreases infarct size of brain, even after the ischemia [93].

Glutathione (GSH)

Glutathione prevent damage caused by reactive oxygen species such as peroxides and free radicals due to the presence of antioxidant properties [94]. According to preclinical studies, glutathione mono-ethyl ester exhibit neuroprotective effect and it useful in the cerebral ischemia treatment. Glutathione reduces infarct size as defensive antioxidant of cells [73].

Scavenging of free radicals

The antioxidant compounds have particularly thiols, such as lipoic acid and precursors of glutathione which shows antioxidant effect by hydroxyl radicals and scavenge singlet oxygen. Vitamin E and C also work as scavenging that increases the concentration of glutathione. A recent study reported that N-acetylecysteine (NAC) administration protects the brain from injury of free radical with the effective therapeutic window after reperfusion and shows neuroprotective effect [95]. Ginkgo biloba (EGb) and α-lipoic acid (LA) both have an antioxidant action which reduces free radical and increases the cerebral blood flow and showed recently in study have neuroprotective effects [96].

Vitamin E

It is a fat-soluble vitamin and as an antioxidant. It stops the formation of reactive oxygen species when fat undergoes to oxidation [72].

Ascorbic acid

It is a dietary supplement and prevents stress-induced memory impairments and reduces oxidative stress. Vitamin C and ascorbic acid cannot cross the blood brain barrier (BBB) but when it oxidized, produces dehydroascorbic acid

which crosses the blood brain barrier and it is useful in the stroke.

Xanthine oxidase inhibitor

Uric acid concentration in blood increased shows the increased xanthine oxidase activity and increase oxidative stress that cause high level of damage. Xanthine oxidase inhibitor alone or with drugs such as allopurinol, oxypurinol and febuxostat shows a good therapeutic approach for circulating uric acid concentration.

Nitric oxide synthases

Nitric oxide (NO) is produces in brain. NO is an intracellular messenger which attempt as mediator of cell death in normal condition but it does not causes any noxious while as its overproduction which causes ischemia. So in the treatment of stroke selective nitric oxide inhibitor can be used.

Combination therapies

When the drugs were given alone sometime they shows pharmacological effects but in some cases like in stroke, alone drugs effects may be not sufficient for the treatment of the diseases. Therefore, combinations drugs can produce optimize effect. Previously some drugs like aspirin were studied as an antiplatelet agent, who was widely used for the prevention of stroke. Alone aspirin (25mg) according to the trial reduces 15% risk of secondary stroke and in combination with dipyridamole (200mg bid) will reduce 37% risk by various mechanism of action.

A combination treatment was investigated in middle cerebral artery occlusion (MCAO) model with blood brain permeability. In study the IgG- tumor necrosis factor receptor (TNFR) and IgG- glial cell line-derived neurotrophic factor (GDNF) fusion protein were used, where TNFR and GDNF were fused with the chain of a chimeric monoclonal antibody (MAb) which was opposed to the mouse transferring receptor (TfR). The cTfRMAb-GDNF fusion protein alone reduces 30% in cortical stroke volumes and 25% reduces in hemispheric stroke volumes. But when it was treated with combination form with the cTfRMAb-GDNF and cTfRMAb-TNFR fusion proteins which reduces 69%, 54% and 30% in hemispheric, cortical and subcortical stroke volumes [97]. In animal study examined that the combination therapy of angiotensin converting enzyme inhibitor and angiotensin receptor blockers (ARBs) shows better results in the treatment of stroke. In better stroke treatment the ramipril/telmisartan combination can give better BP control and greater cardio-renal protection then alone treatment [76].

Rehabilitation

Rehabilitation describes specialized health care dedicated to improving, maintaining or restoring physical strength, cognition and mobility with maximized results. It involves in various stroke patient mainly focused to improve quality of daily life. Rehabilitation means to help people gain greater independence after illness, surgery or injury [77].
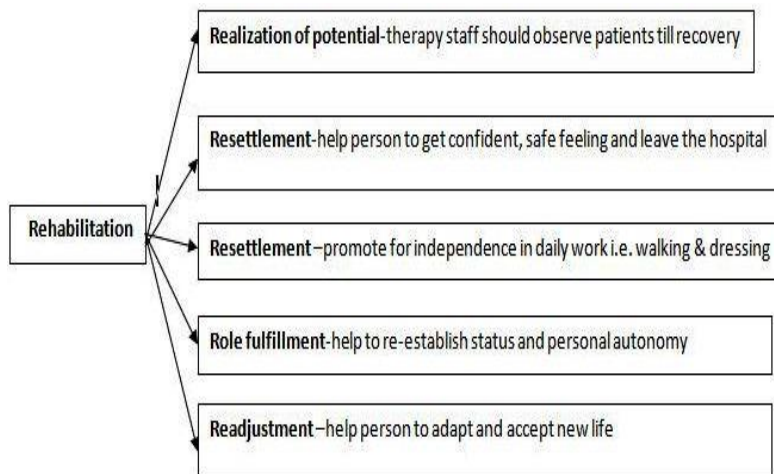

Fig. 4: Rehabilitation

Surgical Treatment

Various new surgical methods for stroke patients with arteriovenous malformation and aneurysms: are offered like stereotactic microsurgery, hypothermia and cerebral revascularization and with this interventional neuroradiology and stereotactic radiosurgery are also offered.

Carotid Endarterectomy

This technique is used to treat or remove atherosclerotic plaque from the carotid artery when the vessel is blocked. For several patients with minor strokes or TIAs this technique has been recently proven and for preventing future strokes this method (carotid endarterectomy) is highly beneficial.

Stereotactic Radiosurgery for Arteriovenous Malformation (AVMs)

The procedure of stereotactic radiosurgery is generally observed on an outpatient basis. This technique as stereotactic microsurgery to identify the exact or precise location of the AVM and if once located the AVM obliterated by focusing a beam radiation which cause it to clot and disappear then. Normal brain tissue is not affected due to the precision of this technique.

Hypothermia

There is a minor risk that the patient may have stroke while on the operating table during the surgical treatment of AVMs and aneurysms, so Stanford physicians are using a hypothermia technique (cooling of the body) which are used to prevent the stroke during the surgical treatment of aneurysms and AVMs. Cardiopulmonary bypass machine special equipment which are used to completely shunt blood flow away from the brain while the body is placed under the deep hypothermia.

Revascularization of the blood supply

To treating the blocked cerebral arteries or aneurysms, revascularization surgical techniques are used. This method is providing a new way (route) of blood to the brain by grafting other vessel to cerebral artery.

Endovascular Treatment of Aneurysms

Endovascular treatment of aneurysms is known as a new interventional neuroradiologic technique that is beneficial for patients with serious medical condition who are inefficient to sustain the stress of surgery. Stanford established Platinum coils which are guided into the aneurysms via a catheter that creating a clot that effectively closes the aneurysm off from surrounding circulation and preventing the future hemorrhagic stroke risk.

Angioplasticity and Stenting of Vessels in the Neck and Brain

Cerebral angioplasticity is similar to the cardiology procedure which is mostly used to open the partially blocked vertebral and carotid arteries in the neck as well as blood vessels within the brain [59].

SUMMARY

The present days stroke is a extremely prevalent health problem and to treat or prevent the stroke, completely desire to understand the pathophysiology that can help to improve the current clinical conditions of stroke and the biomarker reflecting relevant events would also be of great use in the ischemic cascade. By the use of marker in the detection of stroke may require capturing all processes underlying the ongoing ischemic event. A stroke can be diagnosed by the various symptoms including sudden numbness, severe headache, speech difficulty, face dropping. So for the prevention and better treatment of ischemic stroke there are multiple choices are provided such as thrombolytics therapy, antioxidant, hypertension, anticoagulant therapy, rehabilitation technique also and various surgical treatment including such as carotid endarterectomy, stereotactic radiosurgery, hypothermia, revascularization of the blood supply, endovascular treatment of aneurysms and angioplasty and stenting of vessels in the neck and brain are also required for the better treatment of ischemic stroke. There are such combination therapy are also required in recent years for better management that improved the stroke. Combination therapy e.g. Aspirin and clopidogrel, Aspirin and dipyridamole, ramipril and telmisartan, IgG- glial cell-lined derived neurotropic factor (GDNF) and IgG- tumor necrosis factor receptor (TNFR) shows the increased benefit ratio in stroke patients.

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