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Pharmacological Approaches and Management of Brain Stroke

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ABSTRACT
Stroke is a common health problem in present days which is identified by the symptoms including face drooping, speech difficulty, sudden numbness, and sudden trouble in vision, loss of balance or coordination, severe headache. The epidemiological studies have shown about 750,000 people have stroke per year in which 80% have ischemic stroke and remaining 20% have hemorrhagic stroke but there are very few treatments available in present that can treat stroke and their deformities. The rate of morbidity and mortality is higher in stroke and it is 4th leading cause in US and 3rd one in developing countries. Hence a good pharmacological management is required for the better treatment and recovery from stroke. The pharmacological management includes use of thrombolytics, antiplatelet therapy, hypolipedaemics, antihypertensive, antioxidants, clot disruption technique, rehabilitation technique and their combinations such as clopidogrel + aspirin, Aspirin + dipyridamole, telmisartan + ramipril, melatonin + tpa, IgG–glial cell line-derived neurotrophic factor (GDNF) and IgG– tumor necrosis factor receptor (TNFR). Therefore, a variety of combinational studies are required for the more beneficial outcomes in the future.

Keywords: Brain stroke, Ischemia, Combinational therapy.

INTRODUCTION
Stroke is leading cause of death [(1)] in developed countries followed by cancer and cardiac disease, which is common cause of long-term neurological and serious physical disability [(2, 3)]. About 750,000 people have stroke per year, in which 80% have ischemic and remaining 20% have hemorrhagic stroke [(4)]. During the first year after stroke 50% of the patients readmitted or died. Aged patients suffering from other problems and diseases are more capable for adverse events [(5)]. In Stroke the blood supply of brain is obstructed because of ischemia and hemorrhage causes loss of brain functioning. Ischemia causes by blockage in blood vesicles *via* thrombosis, arterial embolism vasoconstriction [(6)] as well as by systemic hypo-perfusion [(7)]. There are two types of risk factors for causing stroke one is controllable and other one is uncontrollable. The controllable risk factors are those which can control by changing in our daily routine. The controllable risk factors includes hypertension, high cholesterol, smoking or tobacco use, diabetes, overweight or obesity, blood disorders, excessive alcohol, and certain drugs (*i.e.* some birth control pills, some anticoagulants). Rather than this the uncontrollable risk factors are difficult to treat and includes age, gender, race, family history, previous stroke or heart attack, transient ischemic attack (TIA), artery abnormalities, arteriovenous malformation, fibro muscular dysplasia and hole in the heart, [(8)]. Some

diseases like chickenpox [9] and infection from some viruses and bacteria also increase the risk of stroke. There are few treatments available for stroke. The FDA approves the tPA as a drug for stroke treatment, which reopens the blocked blood vessels [10]. The tPA must be given within 3 h of stroke for proper therapeutic effect [11]. For the better treatment, recovery and prevention of stroke a good pharmacological management is required, which can also reduce the risk factors of recurrent stroke.

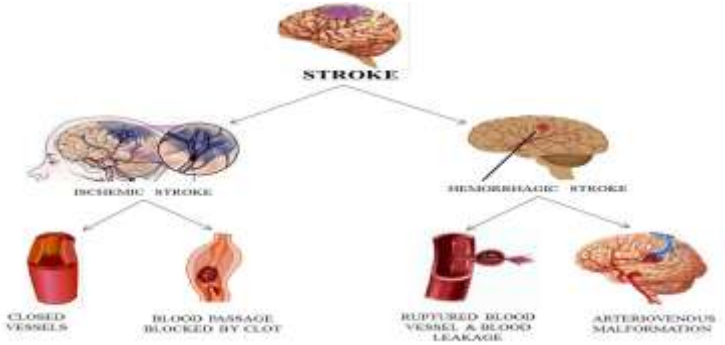

Figure 1. Types of stroke.

MANAGEMENT OF ISCHEMIC STROKE

The ischemic stroke begins with the initial symptoms of neurologic impairment and continues until the impairment stops worsening and the patient stabilizes medically. The duration of the acute phase varies but usually extends from minutes to hours to days. The person who has suffered an acute ischemic stroke can enters in the sub-acute phase, this phase last for weeks to months [12]. The sudden sign of stroke were face drooping, speech difficulty, sudden numbness or weakness of the leg, arm or face, sudden confusion or trouble in understanding, sudden trouble seeing in one or both eyes, sudden trouble in walking, dizziness, loss of balance or coordination, sudden severe headache with no known cause and sudden chest pain [13]. Brain imaging and supplying vessels assessment were required to identify the type and the cause of stroke it may also help to identify the site and cause of arterial obstruction [14]. Ischemia in brain and myocardium are shows common pathological changes so the immediate goals of therapy are given like thrombolytic therapy, antiplatelet therapy, hypercholesterolemia, clot disruption, hypertension treatment therapy and antioxidant therapy. Different therapies of stroke treatment are illustrated in table 1.

Table 1. Some combinational therapies of ischemic stroke.

Stroke treatment	Combinational therapies
Thrombolytic therapy	Plasminogen activators e.g.- Alteplase (tpa), Streptokinase, Reteplase, Tenecteplase [15-18]
Antiplatelet therapy	Aspirin, triflusal, clopidogrel, prasugrel, ticagrelor, ticlopidine[19-23]
Hypercholesterolemia	Statins[24]
Hypertension Treatment	angiotensin type-1 receptor blockers, α-blockers[25]
Antioxidant therapy	Melatonin, Vitamin E, Ascorbic acid, Glutathione, Supenaxide disonutase (SOD), Pyrrolopyrimidines, Supenaxide disonutase, catalasc, glatathione panoxidate, tocophercol[24, 26, 27]
Combination therapy	(clopidogrel + aspirin), (Aspirin + dipyridamole), (telmisartan + ramipril) [28, 29] [30]
Rehabilitation[31]	----
Clot disruption[32]	-----

Different therapies of brain stroke

Thrombolytic therapy

Thrombolytic drugs are used to dissolve blood clots, this process is called thrombolysis and it restricts the damage caused by the blockage in the blood vessel. Thrombolysis is commonly known as clot busting. The most common pathological feature in thrombotic stroke were vascular obstruction called atherosclerosis [(33)]. Atherosclerosis can cause thrombosis and intra-plaque haemorrhage. Thrombolysis with tPA is the approved medical treatment for patients having ischemic stroke. The risk of bleeding can increased if patients have acute ischemic stroke and pretreated with antiplatelet or anticoagulant drugs [(34)]. If thrombolytic agents used properly they can plays an essential role for the successful treatment of stroke [(35)]. Thrombolytic drugs burst the blood clots by activating plasminogen, which forms Plasmin. Plasmin is a proteolytic enzyme that breaks cross-links between fibrin molecules; provides the structural integrity of blood clots. Because of these actions, thrombolytic drugs are also termed as "plasminogen activators" and "fibrinolytic drugs." Plasminogen activators initially used as thrombolytic agents in the acute stroke. They convert plasminogen into plasmin, an enzyme. Plasmin degrade thrombus by breaking fibrinogen, fibrin monomers and cross-linked fibrin which present in thrombus [(15)].

Streptokinase (SK)

It works as plasminogen activators by the formation of SK /plasminogen complex. It is CS-hemolytic streptococci group derived protein that showed significant rates of ischemia and systemic hemorrhage [(16)], but it is not use frequently in acute stroke therapy, instead of this a serine protease urokinase having plasma half-life 14 min is used [(15)]. In 1980's trials of SK was unsuccessful in stroke, because of trial design failure or drug failure. But when other alternatives will not present then it was believed that in a properly design trial it may show beneficial effects on stroke at low dose.[(36, 37)] According to the randomized trial of intra-arterial infusion of urokinase, SK has potency to increase the chance of excellent functional outcome [(38)].

Alteplase (recombinant human tissue-type plasminogen activator; rtPA)

It is a serine protease, having plasma half-life of 3.5 min. It has short half-life and controlled penetration of the clump, because it strongly binds with surface fibrin, and delay restoration of flow which increase the risk of recurrent occlusion. Re-occlusion may be reduces by the administration of heparin or antiplatelet drugs. Furthermore, rtPA have some neurotoxic properties, including activation of metalloproteinase, which may increase permeability of blood–brain barrier that leads to cerebral hemorrhage and edema and arise in calcium currents over the N-methyl-d-aspartate (NMDA) receptor. This causes excitotoxicity and neuronal death [(17)]. Even so rtPA uses in the first line therapy of acute ischemic stroke. If tPA was administer within 3 hours of the initiation of stroke it shows beneficial effect but administration of tPA after three hour show lesser beneficial effects [(39)]. In clinical study on the administration of altipase within 3 hours 59 minutes in randomly assigned 418 patients out of 821 patients and placebo was administered in remaining patient's alteplase treated patients shows favorable results then placebo treated patients. [(40)] According to double blind clinical examination the intravenous alteplase with the dose 0·9 mg/kg bodyweight (maximum dose 90 mg) showed effective results on acute ischemic patients. Initially 10% of total dose will administer as a bolus and then remaining tpa infuse within 60 min. [(41)] [(28)]. Recently licensed plasminogen activators are derived from tPA. These include reteplase, a truncated tPA derivative with a longer half-life and tenecteplase, a bioengineered tPA. A bolus injection of reteplase and tenecteplase can be given due to their longer half-lives [(18)].

Antiplatelet therapy

Antiplatelet drugs inhibit thrombus formation by decreases platelet aggregation in blood. These drugs make alteration in the activation of platelet at the site of vascular damage and prevent development of arterial thrombosis [(42)]. The class of antiplatelet drugs includes in subsections:

Irreversible cyclooxygenase inhibitors

Aspirin-

Aspirin is cyclooxygenase inhibitors and part of non-steroidal anti-inflammatory drug. It shows antiplatelet effect by inhibiting the thromboxane production, which in normal conditions binds platelet molecules with each other to build a patch over damaged blood vessels wall. The platelet patch can be too large and it can obstruct blood flow. Aspirin can use for long-term at low doses, to prevent strokes, heart attacks [43]. Aspirin in low dose (50-325 mg/day) avoid the risk of motility and ischemic injuries in patients suffering from stroke [28] or TIA. [19] Also it has been accepted that aspirin in low doses can be given instantly after a heart attack to reduce the risk of further heart attack or the risk of cardiac tissue death [44] [45]. Some unwanted side effects has been shown mainly in higher dose of aspirin like gastrointestinal ulcers, stomach bleeding, and tinnitus [46].Some other adverse outcomes also shown like in cardiovascular system. [47]

Triflusal

Triflusal (2-acetoxy-4-trifluoromethylbenzoic acid), is a freely used platelet antiaggregant. It has structural similarities to salicylates but it is not derived from aspirin. It inhibits COX-1 and also inhibits COX-2 [20]. When Triflusal administer orally it hydrolyze quickly to its active metabolite 2-hydroxy-4-trifluoromethyl-benzoic acid (HTB), which have power to cross the blood brain barrier it has been recently shown in healthy volunteers [48]. Triflusal reduces risk of hemorrhagic complications and well tolerated in comparison to aspirin [20]. Triflusal and HTB are powerful inhibitors of NF kapp B activation it is studied in In-vitro studies [49] [50].

Adenosine diphosphate receptor inhibitors

Adenosine diphosphate (ADP) inhibitors prevent platelet aggregation via different mechanisms and they are mainly used for the prevention of arterial thrombosis.

Clopidogrel

clopidogrel is a novel ADP-selective agent which has several times higher anti-aggregating properties than ticlopidine. According to recent results its mechanism of action is active only after intravenous or oral administration and there is no circulating activity found in the plasma of treated animals or human volunteers. Experimental study in rats had demonstrate the anti-aggregating activity was caused by metabolites which generates in the liver by cytochrome P450-dependent pathway and by inhibiting ADP to bind with platelet receptors. Several events in the ADP activation process were also inhibited by clopidogrel [21]. According to the previous research study clopidogrel prevent ischemic stroke, either in monotherapy as well as in combination with other antiplatelet agents [51]. Hemorrhage occurrence can be increase when it co-administration with aspirin [52].

Prasugrel

Prasugrel is an inhibitor of platelet aggregation [22]. Prasugrel was investigated as new P2Y12 receptor antagonist who can be used in the treatment of atherothrombosis in patients. Prasugrel requires biologic conversion to the active metabolites for showing the therapeutic action because it is a prodrug. According to the previous studies prasugrel have ability to inhibit ADP-induced platelet aggregation, both selectively and irreversibly and shows greater effects than clopidogrel. On the large randomized, double-blind, double-dummy clinical trial, it was showed that the prasugrel treatment significantly decrease the occurrence of composite endpoint of death from nonfatal stroke which is compared with clopidogrel in patients. Patients having history of stroke or more than 75 years older patients and have the weight more than 60kg will be highly susceptible for the risk of bleeding; the clinical benefit of prasugrel was higher than clopidogrel in the case of higher bleeding rates. Yet the prasugrel did not show a net clinical benefit in the patients having prior stroke or TIA [53].

Ticagrelor

It is a platelet aggregation inhibitor It irreversible antagonizes the adenosine diphosphate (ADP) P2Y12 receptor on platelet [54, 55]. Ticagrelor can show platelet reactivity and give beneficial effects in ischemia stroke [23].

Phosphodiesterase inhibitors

Phosphodiesterases (PDE) mainly *PDE4D* involves in the degradation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) which plays a key role in the smooth muscle cells proliferation so atherosclerosis and plaque stability can be possible [56, 57]. In this case *PDE4D* gene susceptible for stroke [58]. So the phosphodiesterase inhibitors were required.

Rolipram is a selective phosphodiesterase-4 inhibitor mainly targets the phosphodiesterase 4 and comes under the category racetam drugs [59]. Rolipram reduces neuronal damage and shows neuroprotective effects [60]. Rolipram pharmacologically activate cAMP-CREB signaling and enhance neurogenesis after ischemia. Rolipram increases the proliferation of newborn cells in physiologic conditions but in ischemic conditions it decreases the death of new born cell [61].

Glycoprotein IIB/IIIA inhibitors

IIB/IIIA inhibitors work as antiplatelet agent and prevent stroke by mediate platelet aggregation [62]. The inhibitors block the platelet aggregation by antagonizing receptors which binds with fibrinogen molecules and form bridge between touching platelets. So, GP IIb-IIIa inhibitors competitively inhibit fibrinogen and favor endogenous thrombolysis by minimizing thrombus thickening and avert remaking of thrombus. They are useful in the treatment of patients having acute ischemic stroke [63].

Abciximab

It uses to prevent platelets from adhering with each other and forming thrombus (blood clot) within the artery. It is a glycoprotein IIb/IIIa inhibitor. The plasma half-life of abciximab is short because of its stronger affinity to the receptor presents on the platelets; it can be occupy some receptors for weeks but generally in about 96 to 120 hours after the drug discontinuation platelet aggregation returns moderately to the normal. Abciximab targets the glycoprotein IIb/IIIa receptor on the platelet membrane because it is made up of the Fab fragments of an immunoglobulin [64]. According to the previous study for the treatment of acute ischemic stroke abciximab may be safe and effective but in phase 3 study it shows unfavorable benefit-risk [65]. The major side effect of abciximab was periprocedural bleeding [66].

Eptifibatide

Eptifibatide is an glycoprotein IIb/IIIa inhibitor class drug and shows antiplatelet activity [67] for the batter and safer treatment of stroke it can be given with intravenous rt-PA in combination regimen, according to the studies of phase III trial this combination shows safer and effective [68].

Tirofiban

Tirofiban is an antagonist of glycoprotein IIb/IIIa platelet receptor which is highly selective and fast-acting nonpeptide. It has a short plasma half-life time. Glycoprotein IIb/IIIa antagonists were effective in the case of acute coronary syndromes which was proved in large clinical trials. It was also studied in the trials it might be safe in acute moderate ischemic stroke and when administered in a long time after onset of symptom it can be save lives too [69].

Adenosine reuptake inhibitors

Dipyridamole the adenosine reuptake inhibitor inhibits formation of clot and enhance platelet inhibition by magnify the signalling of the NO donor sodium nitroprusside it increases the endothelium-dependent NO/cGMP-mediated signalling and inhibits the cGMP-specific phosphodiesterase. Dipyridamole shows very potent effect in preventing stroke alone and in combination with aspirin [70, 71].

Thromboxane inhibitors

Thromboxane inhibitors acts by inhibiting thromboxane formation and binding of it to the thromboxane receptors, which were G-protein-coupled receptors coupled to the G protein G_q [72] in aspirin resistant patients if aspirin given to the patient the concentration of 11-dehydro thromboxane B2 in urine shows the risk of further stroke at that time thromboxane inhibiter will be used to block thromboxane and reduce the risk of stroke [73]. Stroke may be relieved by selective inhibition of thromboxane synthase and reduces the concentrations

of cerebral TXA2 and promote the cerebral blood flow.[74]

Hypercholesterolemia Treatment

High cholesterol or plaque build-up in the arteries can block normal blood flow to the brain and cause a stroke. High cholesterol may also increase the risk of heart disease and atherosclerosis, which are both risk factors for stroke. Recent studies demonstrate that the statins (reeducates inhibitors) significantly cause reduction in ischemic stroke. Statins decreases risk of stroke by a various mechanisms, like plaque breakdown, by improving homeostasis by enhancing the bioavailability of nitric oxide and by lowering low-density lipoprotein cholesterol. According to experimental study models of ischemic stroke statin therapy lowers infarct size in brain [24].

Hypertension Treatment

Hypertension involves in about 70% of stroke cases [25]. Use of antihypertensive drugs in combination and in alone for the stroke treatment and prevention shows significantly rises effect then last decade [75]. Control of blood pressure will be required for the prevention of secondary stroke and for better recovery after stroke. It is must to control hypertension by applying combination therapy. Recent trials suggest that new hypertensive drugs (angiotensin type-1 receptor blockers (−24%,P=0.0002), α-blockers, new calcium channel blocker) were more effective in stroke prevention then older class drugs (diuretics, β-blocker) [25].

Antioxidant therapy

The highly reactive free radicals and reactive non-radical species are generated constantly in the biological system. When an imbalance occurs between the free radical production and defense power of call against free radicals it causes oxidative stress. At that time free radical reactions causes injury. Oxygen was contained by free radical and reactive non-radical species which were denoted as reactive oxygen species (ROS). After brain injury the production of reactive oxygen species goes high and it causes cellular damage (i.e. lipids, proteins, and nucleic acids) by various molecular pathways and leads to cause cell death [76, 77]. So antioxidants which are endogenous or exogenous compounds [78] will required for preventing or reducing the oxidative stress and reactive oxygen species it can show beneficial effects in the case of cerebral injury and in stroke [79, 80]. Higher concentration of antioxidant in stroke patients can help in surviving after stroke [81]. For the proper action of antioxidant in the treatment of stroke they should require to penetrate the blood brain barrier (BBB) and enter into the brain parenchyma. There are many antioxidants which vary in the crossing of BBB because of their physical properties like lipid solubility (eg, vitamin E) or water solubility (eg, vitamin C). According to the data antioxidant shows neuroprotective effect in the treatment of stroke and stroke-associated oxidative stress [82].

Inhibition of free radical production

There are various molecules that prevent the production of free radicals, XO inhibitors, such as allopurinol or its metabolite oxypurinol, they reduce cerebral infarct volume and act as cytoprotective agents in permanent ischemic brain by blocking purine breakdown, and also by inhibit lipid peroxidation [83, 84]. Oxypurinol also reduce swelling and prevent the neurological deficits [85]. It had already described before that cyclooxygenase-2 (COX-2) involved in ischemic brain injury and in stroke. So cox-2 inhibiters had projected for the study and it shows neuroprotective effects. Mainly nimusulide the selective COX-2 inhibitor reduces cerebral infarction and neurological deficits by inhibiting free radical production [86, 87]. Resveratrol the COX-1 inhibiter also prevents the free radical production and give useful effects in the management of stroke [88].

Pyrrolopyrimidines

It is a novel class of antioxidant which has good properties to penetrate BBB and inhibit lipid peroxidation in brain. It have excellent neuroprotective properties and effective in the case of stroke [89, 90].

Supenaxide dismutase (SOD)

They are enzymes contain antioxidant properties but had unsatisfactory results in experimental stroke

models. So a class of synthetic SOD/catalase, newly reported EUK-134 was examined which shows greater cytoprotective properties and show properties like SOD. It significantly decrease infarct size of brain, these results shows positive effect in the stroke patients, even after the ischemia. According to this study it suggested that synthetic SOD/catalase mimetics effective in the pharmacological management of stroke [(91)].

Glutathione

Glutathione (GSH) contains antioxidant properties and prevents damage which was caused by reactive oxygen species such as free radicals and peroxides [(92)]. Glutathione works as defensive antioxidant of the cells that reduces Infarct size. The glutathione monoethyl ester also shows neuroprotective effect in the preclinical studies and useful in the treatment of cerebral ischemia [(27)].

Scavenging of free radicals

Free radical scavengers are most useful in the prevention and treatment of stroke. The antioxidant compounds particularly thiols, like lipoic acid and the glutathione precursors show its antioxidant effect by scavenge singlet oxygen, and hydroxyl radicals. Vitamin E and C also act by scavenging and increase the levels of glutathione. A recent study shows that on the administration of *N*-acetylcysteine (NAC), it protects brain from the injury of free radical with the effective therapeutic window after reperfusion and shows neuroprotective effect[(93)]. Ginkgo biloba extract (EGb) and α-lipoic acid (LA) are the antioxidant having a variety of actions which may be effecting during stroke. They reduce free radical and increasing cerebral blood flow. Both EGb and LA had showed neuroprotective effects in recent study and showed reductions in stroke infarct volume [(94)].

Melatonin

Melatonin is comes in the category broad-spectrum antioxidant and it is powerful endogenous hydroxyl free-radical scavenger [(95-97)]. According to the previous study melatonin alone or in combination with tPA gives neuronal survival effect by inhibiting caspase-3 activity [(98-100)]. Melatonin also proved a good protection in mitochondrial oxidative stress and effective in the case of stroke [(101)].

Vitamin E

vitamin E is a fat-soluble vitamin. It is an antioxidant and when fat undergoes to oxidation it stops the reactive oxygen species formation [(102, 103)]. Vitamin E supplement reduce the risk of stroke [(26)].

Ascorbic acid

Ascorbic acid is a dietary supplement and according to the study it was suggested that ascorbic acid prevent stress-induced memory impairments and reduce oxidative stress [(104, 105)]. Ascorbic acid or vitamin C cannot cross the blood–brain barrier (BBB) but its oxidized form, dehydroascorbic acid cross blood-brain barrier and useful in the case of stoke [(106, 107)].

Xanthine oxidase inhibitor

Increased uric acid level in blood represents increased xanthine oxidase activity and increase oxidative stress which cause high level of damage. Xanthine oxidase inhibitor alone and with drugs such as allopurinol, febuxostat and oxypurinol, act by dual mechanism which shows a good therapeutic approach for circulating uric acid level and vascular oxidative stress [(108)].

Nitric oxide synthases

Nitric oxide (NO) is an intracellular messenger that is naturally produces in the brain. In normal condition it works as mediater of cell death but it not causes any toxicity while as its overproduction causes toxicity and ischemia [(109)]. So selective nitric oxide inhibitor can be used in the treatment of stroke.

Combination therapies

Some time when drugs were given alone they produce pharmacological effects but in some case like in stroke these effects may be not sufficient for the treatment of the disease. So drugs in combination can produce optimize effect. Some drugs were studied previously like aspirin was studied as an antiplatelet agent that was widely used for the prevention of stroke.

According to the trial in alone aspirin (25 mg) reduces about 15% risk of secondary stroke and in

combination with dipyridamole (200 mg bid) they will reduce 37% risk by different mechanism of action [28, 110, 111].

In a trial of one month on acute large-artery atherosclerosis stroke patient's clopidogrel and aspirin in combination give higher anti platelet activity then aspirin so it can be more effective and safer in the stroke treatment [29].

A combination treatment was studied in middle cerebral artery occlusion (MCAO) model with blood brain permeability. The IgG– tumor necrosis factor receptor (TNFR) and IgG– glial cell line-derived neurotrophic factor (GDNF) fusion protein were used in the study, where GDNF and the TNFR were fused with the chain of a chimeric monoclonal antibody (MAb) opposed to the mouse transferrin receptor (TfR). The cTfRMAb–GDNF fusion protein individually reduces significant 25% in hemispheric and 30% in cortical stroke volumes. When it was treated in combined form with the cTfRMAb–GDNF and cTfRMAb–TNFR fusion proteins it reduces significantly 54%, 69% and 30% in hemispheric, cortical and subcortical stroke volumes. So BBB penetration of IgG–GDNF and IgG–TNFR fusion increases the effect of IgG–GDNF fusion protein [112].

Previous study also suggest that the combination of melatonin with tPA enhances the life-span of neurones by reducing caspase-3 activity [98, 99].

According to the animal study it was suggested that the combination of angiotensin receptor blockers (ARBs) with angiotensin-converting enzyme inhibitors can give better results on stroke treatment. Full dose of telmisartan 1 mg/kg/day and ramipril 4 mg/kg/day was given alone and in combination to the animal rats. The result of study was 83% stroke in control group animals and 56% stroke in ramipril treated group. And there was no strokes found in other groups. the combination of telmisartan/ramipril can give better BP control, greater cardio-renal protection and better stroke treatment then alone treatment [30].

Rehabilitation

Rehabilitation is a set of complex which mainly involve for several of stroke patients mainly aimed to improve quality of daily life from facing difficulties in living because of disease. The main purposes of rehabilitation can be showed as the "five R". First one realization of potential which ensuring that the therapy staff sufficiently observes patient till plateau phase in recovery, second one is resettlement which is for promoting patients to do daily living works freely such as walking and dressing, the third one is resettlement for helping the person to get confident and leave hospital and give support, forth rehabilitation role fulfilment in which a help should give to the person to establish again their status and personal autonomy, and the fifth one is Readjustment in which person should helped to adopt in a new lifestyle. [31]

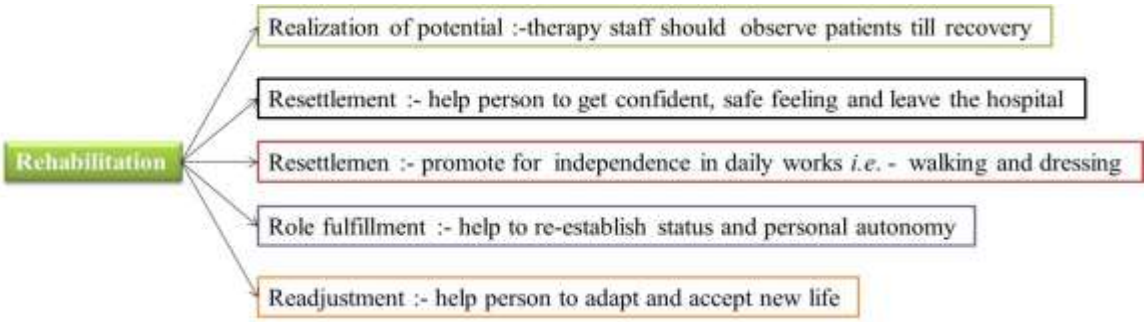

Figure 2. Rehabilitation

Clot Disruption

Clot Disruption can effect safely in intracerebral haemorrhagic condition and decrease mortality rates than other therapies. Early treatment by this technique shows early recanalization in some patients. It improves flow and also decrease the time

of restoration of flow [32]. Mechanical disruption with intra-arterial cerebral thrombolysis would be very unselected stroke still after 6 hours [113].

CONCLUSION

Stroke is a highly prevalent health problem in present days which is diagnose by the symptoms including face drooping, speech difficulty, sudden numbness sudden trouble seeing in one or both eyes loss of balance or coordination severe headache. For the treatment and prevention of ischemic stroke there are multiple choices are available like pharmacological agents and various approaches. These approaches include thrombolytic therapy, antiplatelet therapy, hypercholesterolemia, hypertension, antioxidant therapy; clot disruption and rehabilitation technique too. Extend in therapeutic time window will be important for the treatment of stroke. For the better and safer treatment of stroke a better management will required. In recent years stroke treatment approaches are improved as it includes combination of various categories such as clopidogrel + aspirin, Aspirin + dipyridamole, telmisartan + ramipril, melatonin + tpa, IgG– glial cell line-derived neurotropic factor (GDNF) and IgG– tumor necrosis factor receptor (TNFR). Combination stated in this review shows the increased benefit ratio in stroke patients. Drugs and therapies in combination according to their compatibility and with their good therapeutic responses can give better treatment then the application of single drug. So it requires more combinational studies to perform for the more beneficial outcomes. There remains lot of research and a wide scope for the discovery of different combinational therapy for the secure and effective treatment of PD.

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REFERENCE

[1] World Health O. The top 10 causes of death. World Health Organization website http: www who int/mediacentre/factsheets/fs310/en/index html Accessed September.5.
[2] Flynn RWV, MacWalter RSM, Doney ASF. The cost of cerebral ischaemia. Neuropharmacology. 55, 2008, 250-256.
[3] Martin J, Meltzer H, Elliot D, Britainw G. The prevalence of disability among adults: HM Stationery Office 1988.
[4] Broderick J, Brott T, Kothari R et al. The Greater Cincinnati/Northern Kentucky Stroke Study Preliminary first-ever and total incidence rates of stroke among blacks. Stroke. 29, 1998, 415-421.
[5] Lee H-C, Chang K-C, Huang Y-C et al. Readmission, mortality, and first-year medical costs after stroke. J Chin Med Association. 76, 703-714.
[6] Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. Biochimica et Biophysica Acta (BBA)-Mol Basis Dis. 1802, 2010, 80-91.
[7] Shuaib A, Hachinski VC. Mechanisms and management of stroke in the elderly. CMAJ: Canad Med Assoc J. 145, 1991, 433-443.
[8] Lackland DT, Roccella EJ, Deutsch AF et al. Factors Influencing the Decline in Stroke Mortality A Statement From the American Heart Association/American Stroke Association. Stroke. 45, 2014, 315-353.
[9] Thomas SL, Minassian C, Ganesan V et al. Chickenpox and risk of stroke: a self-controlled case series analysis. Clin Infect Dis. 58, 2014, 61-68.
[10] Doyle KP, Simon RP, Stenzel-Poore MP. Mechanisms of ischemic brain damage. Neuropharmacology. 55, 2008, 310-318.
[11] Green AR, Shuaib A. Therapeutic strategies for the treatment of stroke. Drug disc today. 2006, 681-693.
[12] Jrgensen HS, Nakayama H, Raaschou HO et al. Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. Arch physic med rehab. 76, 1995, 406-412.

[13] Greenlund KJ, Neff LJ, Zheng Z-J et al. Low public recognition of major stroke symptoms. Am j prevent medi. 25, 2003, 315-319.
[14] European Stroke Organisation Executive C, Committee ESOW. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovas dis. 25, 2008, 457-507.
[15] Lisboa RC, Jovanovic BD, Alberts MJ. Analysis of the safety and efficacy of intra-arterial thrombolytic therapy in ischemic stroke. Stroke. 33, 2002, 2866-2871.
[16] Cornu C, Boutitie F, Candelise L et al. Streptokinase in Acute Ischemic Stroke: An Individual Patient Data Meta-Analysis The Thrombolysis in Acute Stroke Pooling Project. Stroke. 31, 2000, 1555-1560.
[17] Kaur J, Zhao Z, Klein GM et al. The Neurotoxicity of Tissue Plasminogen Activator & quest. J Cereb Blood Flow Metab. 24, 2004, 945-963.
[18] [Llevadot J, Giugliano RP, Antman EM. Bolus fibrinolytic therapy in acute myocardial infarction. Jama. 286, 2001, 442-449.
[19] Costa J, Ferro JM, Matias-Guiu J et al. Triflusal for preventing serious vascular events in people at high risk. Cochrane Database Syst Rev. 3, 2005,
[20] Murdoch D, Plosker GL. Triflusal. Drugs. 66, 2006, 671-692.
[21] Nurden PSPNAT, Herbert SL-TJM. Clopidogrel: a review of its mechanism of action. 2009, 251-255.
[22] O'Riordan M. Switching from clopidogrel to prasugrel further reduces platelet function. 2010.
[23] Gurbel PA, Bliden KP, Butler K et al. Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies The RESPOND Study. Circulation. 121, 1188-99.
[24] Vaughan CJ. Prevention of stroke and dementia with statins: effects beyond lipid lowering. Am j cardiol. 91, 2003, 23-29.
[25] Wang JG, Staessen JA, Birkenhger WH. Antihypertensive treatment and prevention of stroke and dementia. Seminars in Cerebrovascular Diseases and Stroke. 2003 Elsevier; 2003. p. 155-164.
[26] Ascherio A, Rimm EB, Hernaỉ • n MA et al. Relation of consumption of vitamin E, vitamin C, and carotenoids to risk for stroke among men in the United States. Annal int med. 130, 1999, 963-970.
[27] Anderson MF, Nilsson M, Eriksson PS, Sims NR. Glutathione monoethyl ester provides neuroprotection in a rat model of stroke. Neurosci lett. 354, 2004, 163-165.
[28] Albers GW, Amarenco P, Easton JD et al. Antithrombotic and thrombolytic therapy for ischemic stroke. CHEST J. 119, 2001, 300S-320S.
[29] Yi X, Lin J, Wang C et al. A Comparative Study of Dual versus Monoantiplatelet Therapy in Patients with Acute Large-Artery Atherosclerosis Stroke. J Stroke Cerebrovas Dis. 7, 2014, 1975-1981.
[30] Zhou Y, Yu F, Ene AR, Catanzaro DF. Telmisartan ramipril combination therapy reduces strokes and improves cardiac and renal protection in stroke prone spontaneously hypertensive rats. J Am Soc Hypert. 1, 2007, 423-432.
[31] Young J, Forster A. Rehabilitation after stroke. Br Med J. 7584, 2007, 86-90.
[32] Noser EA, Shaltoni HM, Hall CE et al. Aggressive Mechanical Clot Disruption A Safe Adjunct to Thrombolytic Therapy in Acute Stroke? Stroke. 36, 2005, 292-296.
[33] Elkind MSV. Inflammatory mechanisms of stroke. Stroke.41, 2010, S3-S8.
[34] Diener H-C, Foerch C, Riess H et al. Treatment of acute ischaemic stroke with thrombolysis or thrombectomy in patients receiving anti-thrombotic treatment. Lancet Neurol. 12, 2013, 677-688.
[35] Hsu Y-W, Liu C-C, Liu I, Choi W-M. Thrombolytic Therapy in Acute Stroke. Int J Gerontol. 2, 2008, 140-142.
[36] Shuaib A, Mohammad A, Sherin A et al. Thrombolysis in the treatment of acute stroke: is there a role for streptokinase when tissue plasminogen activator is not available? J Postgrade Med Inst. 27, 2013, 122-128.
[37] Butcher K, Shuaib A, Saver J et al. Thrombolysis in the developing world: is there a role for streptokinase? Int J Stroke. 8, 2013, .0560-565.

[38] Ogawa A, Mori E, Minematsu K et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. Stroke. 38, 2007, 2633-2639.
[39] Albers GW. Expanding the window for thrombolytic therapy in acute stroke the potential role of acute MRI for patient selection. Stroke. 30, 1999, 2230-2237.
[40] Wahlgren N, Ahmed N, Dvalos A et al. Thrombolysis with alteplase 3 4· 5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet. 372. 2008 1303-1309.
[41] Bluhmki E, Chamorro n, Dvalos A et al. Stroke treatment with alteplase given 3.0 4-5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. Lancet Neuro. 8, 2009, 1095-1102.
[42] Shehab N, Sperling LS, Kegler SR, Budnitz DS. National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus aspirin and from warfarin. Arch int medi. 170, 2010, 1926-1933.
[43] Lewis Jr HD, Davis JW, Archibald DG et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration Cooperative Study. New Engl J Med. 309, 1983, 396-403.
[44] Julian DG, Chamberlain DA, Pocock SJ. A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): a multicentre unblinded randomised clinical trial. Br Med J. 313, 1996, 1429.
[45] Krumholz HM, Radford MJ, Ellerbeck EF et al. Aspirin in the treatment of acute myocardial infarction in elderly Medicare beneficiaries Patterns of use and outcomes. Circulation. 92, 1995, 2841-2847.
[46] Macdonald S. Aspirin use to be banned in under 16 year olds. Br Med J. 325, 2002, 988.
[47] FitzGerald R, Pirmohamed M. Aspirin resistance: effect of clinical, biochemical and genetic factors. Pharmacol therap. 130, 2011, 213-225.
[48] Valle M, Barbanoj MJ, Donner A et al. Access of HTB, main metabolite of triflusal, to cerebrospinal fluid in healthy volunteers. Eur j clin pharmacol. 61, 2005, 103-111.
[49] De Arriba AFn, Cavalcanti F, Miralles A et al. Inhibition of cyclooxygenase-2 expression by 4-trifluoromethyl derivatives of salicylate, triflusal, and its deacetylated metabolite, 2-hydroxy-4-trifluoromethylbenzoic acid. Mol pharmacol. 55, 1999, 753-760.
[50] Bayn Y, Alonso As, Crespo MSn. 4 trifluoromethyl derivatives of salicylate, triflusal and its main metabolite 2 • hydroxy • 4 trifluoromethylbenzoic acid, are potent inhibitors of nuclear factor B activation. Br j pharmacol. 126, 1999, 1359-66.
[51] Rodriguez YM, Arias RS, Fernndez FJ et al. [Clopidogrel and stroke]. Revista de neuro. 53, 2011, 561-573.
[52] Diener HC, Bogousslavsky J, Brass LM. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): Randomized, double-blind, placebo-controlled trial. ACC Cur J Rev, 13, 2004, 331-337.
[53] Baker WL, White CM. Role of prasugrel, a novel P2Y12 receptor antagonist, in the management of acute coronary syndromes. Am j cardiovas drugs. 9, 2009, 213-229.
[54] Jacobson KA, Boeynaems JM. P2Y nucleotide receptors: promise of therapeutic applications. Drug disc today. 15, 2011, 570-578.
[55] Schmig A. Ticagreloris there need for a new player in the antiplatelet-therapy field. N Engl J Med. 361, 2009, 1108-1111.
[56] Gulcher JR, Gretarsdottir S, Helgadottir A, Stefansson K. Genes contributing to risk for common forms of stroke. Trends mol med. 11, 2005, 217-224.
[57] Naghavi M, Libby P, Falk E et al. From vulnerable plaque to vulnerable patient a call for new definitions and risk assessment strategies: part I. Circulation. 108, 2003, 1664-1672.
[58] Munshi A, Kaul S. Stroke genetics focus on PDE4D gene. Int J Stroke. 3, 2008, 188-192.

[59] Zhu J, Mix E, Winblad B. The antidepressant and antiinflammatory effects of rolipram in the central nervous system. CNS drug rev. 7, 2001, 387-398.
[60] Block F, Schmidt W, Nolden-Koch M, Schwarz M. Rolipram reduces excitotoxic neuronal damage. Neuroreport. 12, 2001, 1507-1511.
[61] Sasaki T, Kitagawa K, Omura-Matsuoka E et al. The phosphodiesterase inhibitor rolipram promotes survival of newborn hippocampal neurons after ischemia. Stroke. 38 2007, 1597-1605.
[62] Choudhri TF, Hoh BL, Zerwes H-G et al. Reduced microvascular thrombosis and improved outcome in acute murine stroke by inhibiting GP IIb/IIIa receptor-mediated platelet aggregation. J Clin Invest. 102, 1998, 1301-1310.
[63] Ciccone A, Abraha I, Santilli I. Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke. Cochrane Database Syst Rev. 4, 2006, 392-394
[64] Ch CC. International Nonproprietary Names for Pharmaceutical Substances. WHO Drug Information. 1, 1987,
[65] Adams HP, Effron MB, Torner J et al. Emergency Administration of Abciximab for Treatment of Patients With Acute Ischemic Stroke: Results of an International Phase III Trial Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). Stroke. 39, 2008, 87-99.
[66] Petronio AS, Musumeci G, Limbruno U et al. Abciximab improves 6-month clinical outcome after rescue coronary angioplasty. Am heart j. 143, 2002, 334-41.
[67] Gribble GW, Badenock JC. Heterocyclic Scaffolds II: Reactions and Applications of Indoles: Springer. 2010,
[68] Pancioli AM, Adeoye O, Schmit PA et al. Combined Approach to Lysis Utilizing Eptifibatide and Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke Enhanced Regimen Stroke Trial. Stroke. 44, 2013, 2381-2387.
[69] Siebler M, Hennerici MG, Schneider D et al. Safety of tirofiban in acute ischemic stroke the SaTIS trial. Stroke. 42, 2388-2392.
[70] Aktas B, Utz A, Hoenig-Liedl P et al. Dipyridamole enhances NO/cGMP-mediated vasodilator-stimulated phosphoprotein phosphorylation and signaling in human platelets in vitro and in vivo/ex vivo studies. Stroke. 34, 2003, 764-769.
[71] Albers GW, Amarenco P, Easton JD et al. Antithrombotic and thrombolytic therapy for ischemic stroke the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. CHEST J. 126, 2004, 483S-512S.
[72] Abe T, Takeuchi K, Takahashi N et al. Rat kidney thromboxane receptor: molecular cloning, signal transduction, and intrarenal expression localization. J Clin Invest. 96, 1995, 657-664.
[73] Eikelboom JW, Hirsh J, Weitz JI et al. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation. 105, 2002, 1650-1655.
[74] Pettigrew LC, Grotta JC, Rhoades HM, Wu KK. Effect of thromboxane synthase inhibition on eicosanoid levels and blood flow in ischemic rat brain. Stroke. 20, 1989, 627-632.
[75] Ovbiagele B, Ernstrom K, Markovic D, Raman R. Trends in Antihypertensive Drug Prescription Patterns among Ambulatory Stroke Patients in the United States,. J Stroke Cerebrovas Dis. 22, 2000-2009, e568-e575.
[76] Alexandrova ML, Bochev PG. Oxidative stress in stroke. Oxidat Stress Neurodegen Dis. 1, 2007, 313-368.
[77] Gilgun-Sherki Y, Rosenbaum Z, Melamed E, Offen D. Antioxidant therapy in acute central nervous system injury: current state. Pharmacol rev. 54, 2002, 271-284.
[78] Delanty N, Dichter MA. Antioxidant therapy in neurologic disease. Arch neuro. 57, 2000, 1265-1270.
[79] Sies H. Oxidative stress: oxidants and antioxidants. Experimental physiology. 82, 1997, 291-295.

[80] Wolf G. The discovery of the antioxidant function of vitamin E: the contribution of Henry A. Mattill. J nut. 135, 2005, 363-366.
[81] Ha L, Sakhi AK, Bhn SKl et al. Antioxidant status after an acute stroke and the association with survival in elderly at nutritional risk. Eur e-J Clin Nut Metab. 6, 2011, e135-e141.
[82] Leinonen JS, Ahonen J-P, Lnnrot K et al. Low plasma antioxidant activity is associated with high lesion volume and neurological impairment in stroke. Stroke. 31, 2000, 33-39.
[83] Lindsay S, Liu TH, Xu JA et al. Role of xanthine dehydrogenase and oxidase in focal cerebral ischemic injury to rat. Am J Physiol-Heart Circ Physiol. 261, 1991, H2051-H2057.
[84] Soloniuk DS, Perkins E, Wilson JR. Use of allopurinol and deferoxamine in cellular protection during ischemia. Surg neurol. 38, 1992, 110-113.
[85] Lin Y, Phillis JW. Oxypurinol reduces focal ischemic brain injury in the rat. Neurosci let. 126, 1991, 187-190.
[86] Candelario JE, Gonzlez FA, Garca CM et al. Wide therapeutic time window for nimesulide neuroprotection in a model of transient focal cerebral ischemia in the rat. Brain res. 1007, 2004, 98-108.
[87] Candelario JE, Alvarez D, Merino N, Len OS. Delayed treatment with nimesulide reduces measures of oxidative stress following global ischemic brain injury in gerbils. Neurosci res. 47, 2003, 245-253.
[88] Candelario JE, De OACP, Gr S et al. Resveratrol potently reduces prostaglandin E2 production and free radical formation in lipopolysaccharide-activated primary rat microglia. J neuroinflam. 4, 2007, 25.w
[89] Schmid ER, Zausinger S, Hungerhuber E et al. Superior neuroprotective efficacy of a novel antioxidant (U-101033E) with improved blood-brain barrier permeability in focal cerebral ischemia. Stroke. 28, 1997, 2018-2024.
[90] Andrus PK, Fleck TJ, Oostveen JA, Hall ED. Neuroprotective effects of the novel brain • penetrating pyrrolopyrimidine antioxidants U101033E and U104067F against post • ischemic degeneration of nigrostriatal neurons. J neurosci res. 47, 1997, 650-654.
[91] Baker K, Marcus CB, Huffman K et al. Synthetic combined superoxide dismutase/catalase mimetics are protective as a delayed treatment in a rat stroke model: a key role for reactive oxygen species in ischemic brain injury. J Pharmacol Exp Theraput. 284, 1998, 215-221.
[92] Pompella A, Visvikis A, Paolicchi A et al. The changing faces of glutathione, a cellular protagonist. Biochem pharmacol. 66, 2003, 1499-1503.
[93] Khan M, Sekhon B, Jatana M et al. Administration of N • acetylcysteine after focal cerebral ischemia protects brain and reduces inflammation in a rat model of experimental stroke. J neurosci res. 76, 2004, 519-527.
[94] Clark WM, Rinker LG, Lessov NS et al. Efficacy of antioxidant therapies in transient focal ischemia in mice. Stroke. 32, 2001, 1000-1004.
[95] Shida CS, Castrucci AML, Lamy • Freund MT. High melatonin solubility in aqueous medium. J pineal res. 16, 1994, 198-201.
[96] Allegra M, Reiter RJ, Tan DX et al. The chemistry of melatonin's interaction with reactive species. J pineal research. 34, 2003, 1-10.
[97] Baydas G, Canatan H, Turkoglu A. Comparative analysis of the protective effects of melatonin and vitamin E on streptozocin • induced diabetes mellitus. J pineal res. 32, 2002, 225-230.
[98] Kilic Ã, Kilic E, Reiter RJ et al. Signal transduction pathways involved in melatonin • induced neuroprotection after focal cerebral ischemia in mice. J pineal res. 38, 2005, 67-71.
[99] Kilic E, Kilic, Yulug B et al. Melatonin reduces disseminate neuronal death after mild focal ischemia in mice via inhibition of caspase • 3 and is suitable as an add • on treatment to tissue • plasminogen activator. J pineal res. 36, 2004, 171-176.
[100] Kilic E, zdemir YGr, Bolay H et al. Pinealectomy aggravates and melatonin administration attenuates brain damage in focal ischemia. J Cereb Blood Flow Metab. 19, 1999, 511-516.

[101] Lowes DA, Webster NR, Murphy MP, Galley HF. Antioxidants that protect mitochondria reduce interleukin-6 and oxidative stress, improve mitochondrial function, and reduce biochemical markers of organ dysfunction in a rat model of acute sepsis. Br j anaesth. 110, 2013, 472-480.

[102] Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. J physiol biochem. 57, 2001, 43-56.

[103] Packer L, Weber SU, Rimbach G. Molecular aspects of tocotrienol antioxidant action and cell signalling. J nutr. 131, 2001, 369S-373S.

[104] Kumar RS, Narayanan SN, Nayak S. Ascorbic acid protects against restraint stress-induced memory deficits in Wistar rats. Clinics. 64, 2009, 1211-1217.

[105] Padayatty SJ, Katz A, Wang Y et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. J Am College Nut. 22, 2003, 18-35.

[106] Huang J, Agus DB, Winfree CJ et al. Dehydroascorbic acid, a blood "brain barrier transportable form of vitamin C, mediates potent cerebroprotection in experimental stroke. Proc Nat Acad Sci. 98, 2001, 11720-11724.

[107] Cherubini A, Ruggiero C, Polidori MC, Mecocci P. Potential markers of oxidative stress in stroke. Free Rad Biol Med. 39, 2005, 841-852.

[108] Higgins P, Ferguson LD, Walters MR. Xanthine oxidase inhibition for the treatment of stroke disease: a novel therapeutic approach. Expert rev cardiovas therap. 9, 2011 399-401.

[109] Eliasson MJL, Huang Z, Ferrante RJ et al. Neuronal nitric oxide synthase activation and peroxynitrite formation in ischemic stroke linked to neural damage. J neurosci. 19, 1999, 5910-5918.

[110] Diener HC, Cunha L, Forbes Ce et al. European Stroke Prevention Study 2 Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J neurol sci. 143, 1996, 1-13.

[111] Chaturvedi S. Acetylsalicylic acid extended-release dipyridamole combination therapy for secondary stroke prevention. Clin therapeut. 30, 2008, 1196-1205.

[112] Sumbria RK, Boado RJ, Pardridge WM. Combination stroke therapy in the mouse with blood brain barrier penetrating IgG GDNF and IgG TNF decoy receptor fusion proteins. Brain rese. 1507, 2013, 91-96.

[113] Barnwell SL, Clark WM, Nguyen TT et al. Safety and efficacy of delayed intraarterial urokinase therapy with mechanical clot disruption for thromboembolic stroke. Am j neuroradiol. 15, 1994, 1817-1822..