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 thrombolitics, 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, fibromuscular 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.

**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.

**Figure 1.** Types of stroke.

**Table 1.** Some combinational therapies of ischemic stroke.

<table>
<thead>
<tr>
<th>Stroke treatment</th>
<th>Combinational therapies</th>
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<tbody>
<tr>
<td>Thrombolytic therapy</td>
<td>Plasminogen activators e.g.- Alteplase (tpa), Streptokinase, Retepase, Tenecteplase</td>
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<tr>
<td></td>
<td>(15-18)</td>
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<tr>
<td>Antiplatelet therapy</td>
<td>Aspirin, triflusal, clopidogrel, prasugrel,</td>
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<tr>
<td></td>
<td>ticagrelor, ticlopidine (19-23)</td>
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<td>Hypercholesterolemia</td>
<td>Statins (24)</td>
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<tr>
<td>Hypertension Treatment</td>
<td>angiotensin type-1 receptor blockers, α-blockers (25)</td>
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<tr>
<td>Antioxidant therapy</td>
<td>Melatonin, Vitamin E, Ascorbic acid, Glutathione, Supenaxide disonutase (SOD),</td>
</tr>
<tr>
<td></td>
<td>Pyrrolopyrimidines, Supenaxide disonutase, catalasc, glutathione panoxidate,</td>
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<td>toophercol (24, 26, 27)</td>
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<tr>
<td>Combination therapy</td>
<td>(clopidogrel + aspirin), (Aspirin + dipyridamole), (telmisartan + ramipril) (28, 29)</td>
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<tr>
<td>Rehabilitation</td>
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<td>Clot disruption</td>
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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 play 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 alteplase 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-acetoxo-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 kappa B activation it is studied in ln-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 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 inhibitors 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 inhibitor 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 \(^{(89, 90)}\). 

**Superoxide 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 stroke (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 mediator 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)

**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
neutrotic 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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