ABSTRACT
Ischemic stroke is a leading cause of death and permanent disability. This disease may affect any age group and especially in old age and pregnancy. All the responsible mechanisms are yet not completely understood. There is limited therapeutic intervention beyond prevention, yet tremendous progress in understanding cause of stroke at molecular level has been going on. A lot of advancement has occurred in the prevention and treatment of stroke during the past decade. In this review an update work of causeways of stroke and its therapeutic approaches have been discussed. The relevance of excitotoxicity (role of glutamate receptor), inflammation, ischemic penumbra, apoptosis, to delayed mechanisms and, damage and treatment strategies have been hasted out. Although the results among clinical studies, conflict regarding several experimental data of different therapies, and it may improve neurological outcome after acute cerebral ischemia. Along this several other interventions and new technologies such as stroke detector microwave helmet are being assessed and many other advanced techniques developed by researchers. Even the development of other novel and new treatment strategies (regarding molecular pathways and risk to benefit therapeutic ratio) for stroke are still required in future for better treatment.

INTRODUCTION
Stroke or brain hemorrhage or brain attack is the third leading cause of death in UK, and yet most of the people are unknown of their cause (Rink and Khanna, 2011). The sudden loss of brain functioning probably due to rapid blood supply disturbances in the brain or any blood vessels burst in brain (due to thrombosis or embolism). It is a very severe emergency and cause permanent neurological damage and also death (Moskowitz et al., 2010; Rink and Khanna, 2011). The warning signs of brain attack are: weakness in the face or limbs especially on one side of the body, trouble for talking and understanding to someone, sudden problem in vision, loss of balance and trouble in walking. Sometimes the warning signs may see only in few seconds with nausea and vomiting and then disappear. This type of attack is known as transient ischemic disease (TIA) or mini stroke. There are two major mechanisms which causing brain damage in stroke are ischemia and hemorrhage. On the basis of these mechanism stroke is classified especially in two types (1) Ischemic stroke and (2) hemorrhagic stroke. In different types of stroke, ischemic stroke covers 80% of all strokes, because of unavailability of energy sources such as oxygen, glucose etc. In ischemic stroke a sudden occlusion of blood vessels either embolism or thrombus forms which inhibits the oxygen and nutrient supply to brain. In hemorrhagic stroke there will be rupture in blood vessels supplying to brain (Fig. 1). Besides these two types of stroke other types are also recognized and classified on the basis of Trial of Org 10 172 in Acute Stroke Treatment (TOAST) criteria: (1) Large-artery atherosclerosis (LAA) (embolus or thrombosis), (2) Cardioembolism (CE) (high-risk or medium-risk), (3) small-artery occlusion (SAO) (lacune), (4) stroke of other determined cause (OC), (5) stroke of undetermined cause (UND) (Adams et al., 1993; Goldstein et al., 2001).

In our body many excitotoxic mechanisms intervenes and many of receptors like glutamate and others involved in these ones and releases Ca$^{2+}$ over. When the Ca$^{2+}$ level surmounts its native line the excitotoxicity follows ischemia in different molecular pathways. The t-PA is only approved treatment of stroke at present (Chimowitz; Simoons et al., 1993) but many clinical trials are being in different drugs. Besides this treatment now the scientific team developing new treatment...
strategies for ischemic stroke and other types of strokes. Among those the scientists adopted especially two mechanism first one is neuro-protection and second one is neuro-recovery. In last 2 decades scientific community was focused in discovering and developing neuroprotective agents, but failure in phase 3 trial and investigation of newer approaches has been going on (Sahota and Savitz, 2011). Besides these strategies scientist discovers such devices those find out ischemic area in particular position and other specific strategies to find out different molecular causeways of ischemic stroke.

**PATHOPHYSIOLOGY OF ISCHEMIC STROKE**

**Ischemic Penumbra or Peri-infarct Zone**

Penumbra is the tissue surrounding the ischemic core part where too low blood supply fails to maintain electrical activity but have energy to survive for short period. On the basis of physiology the ischemic brain is classify in different parts: 1) the unaffected tissue, 2) oligemic tissue (tissue at not risk: mild hypoperfused tissue, 3) ischemic penumbra (tissue at risk), 4) the ischemic core (already damaged tissue) (Lee et al., 2005). Normal cerebral blood flow (CBF) is approximately 50-to 60ml/100g/min and fluctuates in different parts of the brain. After reducing the CBF, below 20 ml/100g/min, there is an electrical silence ensues and synaptic activity is significantly diminished in an attempt to preserve energy stores. The CBF of under 10ml/100g/min outcomes in irreversible neuronal injury (Heros, 1994; Schwab et al., 1997; Zivin and Choi, 1991). Recently the CBF is not only the capable measurement of stroke; along this multi-neurocritical stroke therapies (endovascular therapy, electro-acupuncture therapy), have been developed (Broderick et al., 2013; Zhou et al., 2013). Penumbra tissue is the target for interventional therapy in acute ischemic stroke because of having potential for recovery (Heiss, 2000; Hussain et al., 2012; Ramos-Cabrera et al., 2011). With time the therapeutic opportunity lost due to expansion of ischemic core into ischemic penumbra by spreading depolarization from ischemic core to penumbra. The repetitive depolarization around ischemic core appears as peri-infarct depolarization, this causes the expansion of ischemic core forms penumbra or peri-infarct zone. In healthy tissue the peri-infarct depolarization is blocked by NMDA receptor antagonists but in penumbra its recruits the necrosis. Therefore in patients penumbra detection may be increase the treatment possibility (Dreier, 2011).

**Causes of Stroke**

There are many reasons to stroke attack but some reasons are summarized in Table 1. To avoiding stroke we have to make over our life with good habits of eating. There are many reasons of our eating behavior which can indirectly cause stoke by increasing hypertension, glucose level and dyslipidemia. About 85% of all strokes are cause by ischemia. Ischemia is a cascade of events starts from energy cutting down to cell death. As many of the artery abnormalities like atherosclerosis, thrombosis or abnormalities in heart causes deficient supply to brain. Ultimately weakness in blood vessels inside the brain occurs due to diminished nutrient supply following cell death or brain attack. There are different causes of ischemic stroke due to most frequent site of
Microorganisms infections  
Causes: Microorganisms infections
Outcomes: fever, rash
References: (Dnes et al., 2014; Fugate et al., 2014)

Herpes zoster  
Causes: Herpes zoster
Outcomes: Stroke and TIA
References: (Breuer et al., 2014)

Intrapulmonary shunt  
Causes: Intrapulmonary shunt
Outcomes: 523 patients: in the Stroke (85/523) as compared to the Control (34/351)
References: (Bhatia et al., 2013)

Autopsy  
Causes: Autopsy
Outcomes: 58 patients: 12 patients
References: (Hinduja et al., 2013)

Spontaneous calcific embolism  
Causes: Spontaneous calcific embolism
Outcomes: In 71-year-old: rare cause
References: (Acha et al., 2009)

Hypertension  
Causes: Hypertension
Outcomes: In 12,479 participants Risk factor 1.25 (0.94 – 1.65)
References: (Irvin et al., 2014)

Left Ventricular Hypertrabeculation  
Causes: Left Ventricular Hypertrabeculation
Outcomes: 144 patients: 15% having stroke/embolism
References: (Stillberger et al., 2011)

Diabetes  
Causes: Diabetes
Outcomes: In 64 cohort study: 2·28 (95% CI 1·93–2·69) in women and 1·83 (1·60–2·08) in men
References: (Peters et al., 2014)

Smoking  
Causes: Smoking
Outcomes: 5797 stroke survivors: mortality rate 1.36; 95% confidence interval
References: (Levine et al., 2014)

Atherosclerosis  
Causes: Atherosclerosis
Outcomes: 33 stroke patients: Atherosclerotic stroke was defined in 15 (45%)
References: (Lee et al.; 2011)

Contraceptives  
Causes: Contraceptives
Outcomes: 1018 young women: Odd ratio 7.5, 95% CI, 3.6-15.7
References: (Andersson et al., 2012; Roach et al., 2015)

Dyslipidemia  
Causes: Dyslipidemia
Outcomes: 1 568 patients: serum levels of TC, LDL-C, and HDL-C; ORs and 95% CI were 3.01 (1.2, 7.2)/2.6 (1.2, 5.4), 3.15 (1.3, 7.6)/3.4 (1.6, 7.1), and 0.48 (0.24, 0.94)/0.51 (0.2, 0.92),
References: (Xu et al., 2015)

Intracranial atherosclerosis  
Causes: Intracranial atherosclerosis
Outcomes: 131 patients: ICA found in stroke patients (OR, 4.63; P = .032)
References: (Alexander et al., 2014)

Atrial fibrillation  
Causes: Atrial fibrillation
Outcomes: 14,624 patients: anticoagualant (warfarin) is better. An increased risk of stroke was observed in Rivaroxaban
References: (Patel et al., 2013)

Hyperhomocysteinemia and Vitamins Depletion  
Causes: Hyperhomocysteinemia and Vitamins Depletion
Outcomes: Autoimmune disease and stroke
References: (Lazzerini et al., 2007)

Fig. 2: Atrial and cardiac abnormalities causing ischemic stroke
atrial and cardiac abnormalities are shown in Figure 2 (Gonzalez et al., 2011; van der Worp and van Gijn, 2007). Due to so many mechanisms of causing stroke there are different types of stroke such as cardiac embolic stroke, large artery atherosclerotic stroke and varieties of treatment strategies. Recently many researches and clinical trials successfully aimed on treating individual stroke subtypes rather than indiscriminately grouping all strokes together. ‘Intracranial atherosclerosis’ affects the cerebral arteries and blood flow diminished in brain (Wong, 2006). Another cause of stroke is ‘atrial fibrillation’ a common type of arrhythmia. In atrial fibrillation blood pools in the atria and does not pumped completely into the ventricle, so that both the heart’s chamber does not work together (Gold et al., 1986; Wolf; Wyse et al., 2002). The left ventricular thrombosis (blood clot in left ventricle) a common cause occurs after acute interior myocardial infarction and dilated cardiomyopathy and leads to thromboembolic events such as cerebrovascular accidents/stroke (Delewi et al., 2012; Stokman et al., 2001).

In a pilot study in Thailand the stroke risk was assessed in 99 patients in with mean age of 40 ± 8 years were included. The stroke was classified on criteria as and found the common risk factor such as hypertension (HT), diabetes mellitus (DM), Hyperlipidemia (HL), Coronary artery disease (CAD), Previous ischemic stroke (PIS)/TIA, Atrial fibrillation (AF), Valvular heart disease (VHD) (Fig. 3B) in age of between 31–40 and 41–50. The different types of stroke were also detected in age of between 31–40 and 41–50 (Fig. 3A) frequency occurs (Dharmasaroja et al., 2011).

From the findings it may concluded that the occurrences of TIA, LAA and OC type of stroke was higher in age of 31–40 years compared with 41–50 years in which SAO, CE and UND was higher. Rather than this the causing problems of stroke such as HT, DM, CAD, PIS/TIA and AF were higher in age of 41–50 years except HL and VHD (Fig. 3B) higher in 31–40 years of age.

THE MOLECULAR MECHANISM INVOLVED IN PATHOGENESIS OF STROKE

Glutamate and Calcium Overload

The glutamate receptor based therapeutics is extensively involved in treatment of stroke by using glutamate receptor antagonists. Some of the glutamate antagonist therapies against stroke were failed in clinical trials and mostly gave positive results less efficiently (Ginsberg, 2009). The cerebral ischemia occurs due to interstitial ionic imbalance (Turner et al., 2013). Although the calcium is the necessary ion for the communication of the cell and survival, its imbalances triggers the cell death (Annunziato et al., 2007) and ischemia (Bano and Nicotera, 2007). In 19s decade, Benveniste et al. reported that glutamate receptor has major involvement of calcium overload during ischemic stroke (Benveniste et al., 1988). When there is hypoxic or ischemic condition the glutamate receptors excessively activated. The glutamate receptors are specifically two types (1) inotropic glutamate receptors and (2) metabotropic glutamate receptors (Fig. 4) with specific agonists. The extracellular glutamate level
is increased by two basic mechanisms: (1) increased efflux of glutamate at initially Ca\(^{2+}\) dependent and (2) decreased uptake of glutamate. At later stages of ischemia, efflux of glutamate is Ca\(^{2+}\) independent and works in reverse mode (Lau and Tymianski, 2010; Nishizawa, 2001). N-methyl-d-aspartate (NMDA) glutamate receptor play a major role in neurotoxicity (Fig. 5), in contrast to further two ionotropic glutamate receptors (AMPA and Kainate receptors) because later ones are impermeable to Ca\(^{2+}\) and require more time to activate even several hours and take more time to produce neurotoxicity (Carriedo et al., 2000; Lau and Tymianski, 2010; You et al., 2010). The glutamate transmitter overload, increase the Ca\(^{2+}\) entry via glutamate receptors subtypes and along other stored organelles like mitochondria, endoplasmic reticulum and others. This overload of glutamate and Ca\(^{2+}\) causes the neuron death. The NMDA receptors are positioned in different spaces of cell membrane. The locations deter-
mines the excitotoxicity of NMDA receptor; synaptic (necessary for neuronal growth) and extra synaptic (involved in cell death) (Liu et al., 2007).

There are different works which supported the apoptosis and necrotic cell death caused by synaptic glutamate overstimulation (Ankarcrona et al., 1995; Rodríguez et al., 2009; Stout et al., 1998). In NMDA glutamate receptors the Ca\(^{2+}\) entry occurs and if over expressed then the extra Ca\(^{2+}\) is stored in mitochondria and endoplasmic reticulum. In ischemic condition there was highly glutamate expression and Ca\(^{2+}\) entry increased, and excessively expressed (Chen et al., 2008).

**TRPM7 Receptor**

Though the Ca\(^{2+}\) entry through channels like NMDA and AMPA are highly involved in ischemia, and with therapeutic relevance, yet somewhere in clinical trials it shows negative impact (Besançon et al., 2008; Zhang et al., 2012). After that scientist increases more interest towards some non-glutamate receptors like TRPM7 (Jackson et al., 2009; McNulty and Fonfria, 2005; Shapovalov et al., 2011). The mitochondrial overload of Ca\(^{2+}\) increased oxidative phosphorylation and apoptosis and necrotic cell death. Along this Ca\(^{2+}\) changes the nitric oxide synthase (NOS) to nitric oxide (NO) free radicals which also a major factor of neurotic cell death (Noor et al., 2005). NOS in presence of Ca\(^{2+}\) NO forms and later this NO is used in the formation of peroxynitrite (ONOO\(^{-}\)) highly reactive free radicals after combing with superoxide (O\(^{2-}\)) from mitochondria. ONOO\(^{-}\) activates the transient receptor potential melastatin 7 (TRPM7). The TRPM7 is a Ca\(^{2+}\) permeable and non-selective cation channel, involved in brain ischemia (Bae and Sun, 2011; Xiong et al., 2006). Researches show that the Zn\(^{2+}\) ion is highly permeable through TRPM7, and also highly toxic to the cells if concentration increased to physiological level (Galasso and Dyck, 2007; Inoue et al., 2010).

Along with core calcium channels some exchangers and channels also involved in Ca\(^{2+}\) ion entry in cells. The sodium-calcium exchanger exchanges the three Na\(^{+}\) in and one Ca\(^{2+}\) ion out through the cell. But in excitotoxicity case this system reverts (Anunziato et al., 2004).

**Calpains activity**

Non-lysosomal calcium-dependent cysteine proteinases compounds are calpains. On calcium signals they work for remodeling of cytoskeleton, progression of cell cycle, gene expression and programmed cell death (Croall and Ersfeld, 2007). Calpains activity is tightly enforced by endogenous inhibitors Clapastatins (Hanna et al., 2008). The calcium dependent activity of clapains (Fig. 5) (uncontrolled activation) induces the necrotic cell death and tissue damage (Moldoveanu et al., 2003).

**Inflammation**

Cerebral ischemia is occurs by different pathological reactions such as expression of cytokines, adhesion molecules,
chemokines across the activated blood vessel wall, and activation of microglia cells and mediators like prostanoids and nitric oxides occurs immediately (Iadecola and Alexander, 2001; Kleing and Vink, 2009; Lakhan et al., 2009). The post ischemic condition in brain is characterized by inflammation with different changes, such as microglial cells rapid activation and infiltration of circulating inflammatory cells as demonstrated in animal models as well as stroke patients (Jin et al., 2010; Kriz, 2006; Xia et al., 2010). During acute phase of ischemia expression of cytokines and chemokines enhanced and adhesion of intra cellular adhesion molecule-1 (ICAM-1), tumor necrosis factor-α (TNF-α), and many other pathological secretions enhanced (Lambertsen et al., 2009; Luheishi et al., 2011; Park and Bowers, 2010) and other inflammatory cells like DCS and MGs. The secretion of these inflammatory cells after ischemic injury in brain responds to first line defense against it. The brain defense mechanism starts and activation of MMP-9 and reactive species, following production of neurotrophic and protective factors along with immunosuppression (Figure 6). These effects causes brain remodeling and ultimately stroke recovery. Besides these if protective factors fails to recover then infiltration of inflammatory cells, cytokines, chemokines and exhaustive ROS expression find in brain with other damaging mechanisms which leading to stroke (Schroeter and Jander, 2005).

Free radicals overload

As brain consume approximately 20% oxygen of the whole consumption and so produced more free radical than other body parts. Different cardiovascular risk factors enhanced reactive oxygen species (ROS) and nitric oxide species (NOS) in brain and trigger the inflammation and apoptosis, which ultimately causes ischemia (Jin et al., 2010). In systemic and cerebral vascular system the ROS is generated by NADPH oxidase enzyme, xanthene oxidase and mitochondrial enzymes. Along these an enzyme nitric oxide (NOS) synthase is also play a major role in production of free radicals. The NOS reduces the biological activity of NO and causes vasoconstriction with reducing the NO-dependent vascular responses. Reduced bioavailability if NO enhances platelet aggregation, neutrophil infiltration, leukocyte adhesion to vasculature and smooth muscle proliferation leading to inflammation. By increasing the permeability of blood brain barrier, ROS enhances inflammation directly through up regulation of vascular endothelial growth factor (VEGF) and inducing the expression of cytokine, matrix remodeling enzymes and NF-kB activation (Danton and Dietrich, 2003; Moskowitz et al., 2010).

Apoptosis

Apoptosis and necrosis are the major mechanism of cell death after ischemia. Apoptosis is not occurs by single pathway but it enhances or induced by different pathways. Sometimes some aggressive factors/excitotoxicity mechanism involved in apoptosis and sometimes imbalance in biological activities in brain or vascular system reinforced the apoptosis. Mitochondria play a major role apoptosis as reservoir of pro-apoptotic and anti-apoptotic proteins (Vaseva et al., 2012; Wang et al., 2011). From the outer membrane of mitochondria an apoptosis inducing factor (AIF) is released and DNA repair enzyme PARP-1 [poly(ADP-ribose) (PAR) polymerase-1] get activated, leads to “parthanatos,” a kind of cell death (Wang et al., 2011). Apoptosis or neuronal death occurs due to imbalances between Bcl-2 family members. First one is reduces the apoptosis (like Bcl-2 and Bcl-x L) and another (like Bax and Bad) is enhances the apoptosis in brain. In an experiment in rats the heat shock protein-70 (HSP-70) and phosphorylated extracellular-signal-regulated-kinase 1/2 (pERK 1/2 reduces the apoptosis due to influence on Bcl-xL, Bax, and AIF (Liebelt et al., 2010).

Apoptosis is also caused by caspases (cysteine-dependent aspartate-espesifcproteases) major executioners and Apaf-1 (apoptotic protease-activating factor 1) (Friedlander, 2003). In caspases family 14 members have been distinguished, among them 11 are present in human. Stroke is caused by caspase 1, 3, 8, 9, and 11 following release of cytochrome c (Ji et al., 2001; Nakagawa and Yuan, 2000; Youle and Strasser; 2008) Many studies showed that caspases 1 defect mice and caspase 1 and caspase 3 inhibitors treatment were more power of protection against ischemic
Protein conformation play an key role in cell functioning as it imparts new function in cell either it is phosphorylation or dephosphorylating one. Apoptosis is also done by conformational changes in protein due to phosphorylation. A novel enzyme pin 1 is involved in this as its overexpression cause the genetic damage/cancer and apoptosis (Mantovani et al., 2004; Zacchi et al., 2002). Peptidyl-prolyl cis/trans isomerase (PPIase) binds and isomerizes the specific phosphorylated Ser/Thr-Pro (pSer/Thr-Pro) motifs in a subset of proteins, which ensures in conformational changes within the proteins (Lee et al.; Lim et al.). Pin1 can increase cyclin D1 transcription by inflicting three unlike signaling pathways. (1) Growth factor signaling, through Ras, Raf, MAPK/kinase, and lastly targets to the pSer63/73-Pro motifs in c-Jun and multiple pSer/Thr-Pro motifs in c-Fos to activate the activator protein-1 (AP1) (2) Wnt signaling, targets the β catenin (3) cytokine signaling, targets the Nf-κB (Lu and Zhou, 2007).

One another pathway of apoptosis is notch pathway which is initiated by the binding of extracellular domain of Notch to a Notch ligand (Delta and Jagged) (Nefedova et al., 2008). Overexpression of notch ligand Jagged enhances, secretion of interleukin-6 (IL-6), vascular endothelial growth factor, and insulin-like growth factor (Houde et al., 2004) ultimately induces the apoptosis. In mammalian lymphocyte development notch pathway protects the T lymphocyte while away in B lymphocytes cells it activates the apoptosis (Yang et al., 2004). This imposes that in mammalian brain development, notch pathway plays a major role for regulation of apoptosis (Kuan et al., 2000).

![Fig. 8: Risk factor of different types of stroke during and after pregnancy](image)

**INTERRELATIONSHIPS OF STROKE AND VARIOUS PATHOLOGICAL CONDITIONS**

**Interrelationships between Histone Methylation and other Epigenetic Mechanism and Stroke**

Among different epigenetic mechanisms (including: DNA methylation, histone code modifications, nucleosome remodeling, and higher-order chromatin formation, noncoding RNA and RNA editing), histone methylation is an important one due to it regulates and maintains the genomic stability and cellular processes. In our whole life epigenetic mechanisms goes on and play an important role in homeostasis and also some pathophysiological roles if changes occur in normal functioning (Fig. 7). Histones (H1/H5, H2A, H2B, H3 and H4) are the protein in which DNA winds like spool. The enzymes histone methyltransferases, transfer the methyl groups from S-Adenosyl methionine onto the lysine or arginine residues of the N-terminal tails of H3 and H4 histones proteins (Scharff and Imhof). It may repress or suppress the gene and are reversible processes by demethylation of histone depending on site of methylation. Trimethylated histone H3 lysine 9 (H3K9me3) is related with heterochromatin and diminished gene expression, while trimethylated histone H3 lysine 4 (H3K4me3) correlates with euchromatin and increased gene expression (Chisholm et al., 2015; Morris et al., 2010). Compared with histone acetylation, histone methylation does not neutralizes the DNA rather than this it recruit silencing or regulatory proteins that binds methylated proteins by neutralization of positive charge of lysine residue. It may loosen the tail allowing the transcription factors to access the DNA or encompass the tail around the DNA restricting access and modify the chromatin structures (Martin and Zhang, 2005). Some drugs such as valproic acid, trichostatin A, sodium butyrate, SAHA, or MS-275 at appropriate doses possess to preserve histone 3 and 4 acetylation levels during ischemia (Schweizer et al., 2013). Epigenetic drug such as pan-HDACi (histone deacetylases inhibitors) are found promising results in treatment of ischemia. However role of histone methylation rather histone acetylation are poorly understood the enzymes involved in repression of transcription, histone methyltransferases, G9a and SUV39H1 elevate the ischemia (figure 7) and inhibition of these repressive enzymes, induces the gene activation and confer neuroprotection in ischemia (Schweizer et al., 2015).

**Interrelationships Between Angiogenesis and Stroke**

In angiogenesis, the formation of new blood vessels/growth from pre-existing that basically occurs during some physiologic and pathologic disorders (Hayashi et
Interrelationships Between Migraine and Stroke

Transient ischaemic attacks and migraine are both characterized by temporary focal neurological deficits and are little same. Migraine is a nonthreatening disorder that keeps on throughout the life; and affects 3 of 1 female in 12% populations with recurrent attacks of headache, and sometimes proceeded by transient neurological disturbances. The risk of ischaemic stroke was somewhat more than doubled in patients having migraine (Bousser and Welch, 2005). The abnormalities in vasculature (like vasospasm, arterial dissection), and of the blood (including platelet-related hypercoagulability) in migraine could result in ischemic stroke (Gretchen and Tiefjen, 2007). Migraine-related stroke may explicate 25% of the incidence of stroke in persons less than 50 years old (Brodierick and Swanson, 1987). Many biochemical changes appear in acute stroke that seem to have the capacity to arouse an attack in migraine susceptible individuals. For illustration NO (nitric oxide) or glutamate has a major role in the pathophysiology of headache occurring at both stroke and migraine (Heckmann et al., 2002). Syndromes like Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), cerebroretinal vasculopathy, and hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS) has play a major role in clinical features of stroke and migraine (Del Zotto et al., 2008). In two-thirds of patients migraine-like features are observed immediately before and during acute stroke (Nardi et al., 2008). The cause of migraine is the result of low cerebral blood flow and neurally mediated vasodilatation which could cause sluggish flow in large intracerebral vessels during the aura of migraine. This is concluded that migraine-induced stroke usually respects intracranial arterial territories while aura involves more wide spread brain regions. In addition, frequent aura, if due to spreading depression, could induce cytotoxic cell damage and gliosis based on glutamate release or excess intracellular calcium accumulation (Welch, 2003).

Interrelationships Between Pregnancy and Stroke

Stroke and cerebral hemorrhage is a risk factor in pregnancy. The incidence appears to be increasing with stroke causing about 12% of maternal deaths (Roemer et al.). The risk of stroke in pregnancy is raised 13 fold compared with the non-pregnant (Wiebers, 1985) and 80% of stroke had happened in the 2nd and 3rd trimester of pregnancy (Kat suragi et al., 2013) but according to Bellolio et al. stroke has specially occurs in peri-partum state (Fig. 8) (Bellolio et al., 2007). Some of these risk factors consociated with pregnancy-related stroke are: preeclampsia (hypertension: systolic blood pressure of 140 mm Hg or diastolic blood pressure of 90 mmHg), amniotic fluid embolus, postpartum angiopathy and postpartum cardiomyopathy hypertension, diabetes, valvular heart disease, hypercoagulable disorders, sickle cell disease, lupus, abuse of tobacco and other substances, and migraines (Tate and Bushnell). During pregnancy various physiological changes occurs to develop stroke like prothombotic changes, including acquired activated protein C resistance and low levels of free protein S. some other causes of pregnancy induced stroke are cesarean delivery, fluid, infection and electrolyte acid-based disorders. For diagnostic purpose of stroke in pregnancy, head computed tomography (CT) may be used (radiation to the uterus from a routine head CT is <1 mrad; not harmful to foetus) (Helms and Kittner, 2005).

CURRENT TREATMENT STRATEGIES OF STROKE

Magnesium

Magnesium is a neuroprotective in preclinical studies. It had been subjected to embolization of the right middle cerebral artery (MCA) in rats and found positive results (Yang et al., 2000). Many studies have been done in this respect and many clinical trials have in pipeline. Jeffery et al. in a conference showed primary results of 1700 stroke patients phase 3 trial, treated with magnesium therapy ‘FAST-MAG’ and get positive results in treating pre-hospitalization of it (Saver et al., 2014).
G-protein Coupled Estrogen Receptor Antagonists

Some studies show worsening of stroke due to G-protein coupled estrogen receptor (GPER) agonist in males’ and find good results (reduced infarct volume after stroke in male) on treatment with its antagonist. But in ovariectomized females the findings were opposite and concluded that stroke therapy should be done on sex differentiation basis (Broughton et al., 2014).

Tissue plasminogen activator (tPA)

tPA is the treatment which is used by different hospitals to treat stroke and advised to keep it in stores, in emergency conditions (Xian et al., 2014). N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), an endogenously secreting peptide in humans as well as rodents, has cardioprotective and anti-inflammatory potential. In a study AcSDKP combined with tPA and the results were positive. The combination of AcSDKP and tPA as well as alone both, increase the level of AcSDKP and decrease the nuclear transcription factor-κB (NF-κB), transforming growth factor β (TGF-β), and plasminogen activator inhibitor-1 (PAI-1) density (Gavins, 2018; Zhang et al., 2014).

Aspirin/clopidogrel?

Aspirin is used in stroke patients for vascular risk reduction. But in recent studies there are more choices besides aspirin. In the AVERROES double-blinded, randomized trial, 5599 stroke patients participated, who were failed the vitamin K antagonist therapy due to some reasons. Aspirin and Apixaban medicine were given them and compared, the results were consistent (Coppens et al.). In a study patients were treated with 75 mg/day of aspirin and clopidogrel 75 mg/day. In that left ventricular thrombi were noticed in 15 patients during the first 3 months and 2/3 of them left ventricular thrombi were detect within the first week (Solheim et al.). In another randomized, double-blind, placebo-controlled trial conducted in China, the combination of Aspirin and Clopidogrel was assessed. The results were analyzed in 5170 patients within 24 hours having the onset of minor ischemic stroke (MIA) or high-risk TIA and found that the combination results were better than the alone dosing (Wang et al., 2013). Rather than this Lee et al. analyzed the Taiwan National Health Insurance registry, among 2218 patients (age 72 years mean) compared the effectiveness of Clopidogrel vs. Aspirin for vascular risk reduction among ischemic stroke patients. In ischemic patients with ‘aspirin treatment failure’, Clopidogrel was better option than aspirin (Lee et al., 2011). In another double blinded randomized trial, Combination of clopidogrel and aspirin for prevention of recurrence in acute atherothrombotic stroke study was done in 349 patients. They found that both medicine were good for stroke in same manner; no significant difference, but combination treatment of clopidogrel and aspirin was not superior to aspirin alone (Lee et al., 2011). Another study shown that in ischemic stroke aspirin alone could not be efficiently treated (McNamee, 2017).

Dabigatran

Dabigatran is a blood thinner and used in stroke patients with a cost effective manner (Wan et al., 2011). In a study dabigatran bleeding risk factors were compared with warfarin and find that they were similar effective in stroke but the gastric bleeding was 70% high in case of dabigatran (but not other any bleeding type) compared with warfarin (Sarrazin et al., 2014).

Antibiotics

As the stroke is also caused by infection and pneumonia is the most common infection, complicating 1 of 3 cases of acute stroke. Antibiotics are being used as anti-infective agents as well as in neuroprotection (ceftriaxone). A recent conclusion has been come out that the preventative antibiotics show no effect on functional effect or mortality in stroke (Malone et al., 2018). Antibiotics Minocycline and doxycycline superiorly reaches the brain and cerebrospinal fluid and treated stroke efficiently (Koistinaho and Koistinaho). Some other antibiotics also are used in stroke such as moxifloxacin, (Harms et al., 2008), tetracycline (Tikka et al., 2001) which are outdated now. In recently there is an interest in gut micro flora and gut-brain axis for stroke pathology and treatment (Malone et al., 2018).

Use of vitamin C

A study suggests that taking fruits and vegetables containing vitamin C in food may help in treating stroke. Dr. Vannier says there is more research is now needed to confirm the findings. Although vitamin C might reduce stroke risk could be by reducing blood pressure and other benefits also presents (Panel et al., 1997). In another study it was concluded that the consumption of more vegetables and fruits in your diet lowers the risk of stroke in your life (Lee et al., 2014).

Sunlight

Universities of Southampton and Edinburgh in the UK, had conducted a new research in 24 volunteers to ultra-violet by a tanning lamp and suggested that sunlight
reduces the blood pressure, which is a major cause of stroke. The sunlight was reducing the level of nitric oxide in the skin by transferring it from the skin to the circulation (lowering blood vessel tone). The lowering of blood vessel tone decreased the blood pressure following heart attack and stroke (Medina et al., 2015).

**Use of vitamin E**

Medical News Today reported on a study by Dr. Rink and colleagues that vitamin E (tocotrienol) may help in stroke by activated arteriogenesis (an increase in the diameter of existing arteries in response to oxygen demand) by blocking the cholesterol production in the liver and reduce total blood cholesterol (Whiteman, 2017; Wan et al., 2011). In another study it was concluded that there is an inverse proportion between consumption of nut in your diet and stroke risk factor (Afshin et al., 2014).

**OTHER ADVANCEMENT IN STROKE TREATMENT STRATEGIES**

**Strokefinder Microwave Helmet**

Some researchers developed a microwave system (Strokefinder microwave helmet) for the detection of stroke. They have done trial on it and find the successful results on detecting the stroke caused by blood clot or bleeding in brain tissue during the pre-hospitalization (Persson et al., 2014).

**Stem cell-based treatment**

Human induced pluripotent stem cells (iPSCs) are a novel approach to produce patient-specific cells for autologous transplantation. In this study stem cells, generated from adult human fibroblast-derived iPSCs were transplanted in stroke-damaged mouse and rat striatum or cortex. Recovery was started in just seven days and after transplantation. This study was the first evidence of transplantation of human iPSC-derived cells and concluded the safety and efficient approach to promote recovery after stroke by new neurons for replacement in injured brain (Oki et al., 2012). In another study human skin-derived iPSCs were also find to improve neurological outcome after intracortical implantation in a rat stroke model (Tornero et al., 2013). Another interest in dental pulp stem cells (DPSC) was also determine in murine model for enhancing neurological recovery following stroke and traumatic injury recovery. This study was demonstrated the neuronal differentiation of DPSC from murine incisors *in vitro* (Ellis et al., 2014).

**Combination of NCP and VPCs co-transplantation**

The proper functioning of neurovascular unit (interactions between neural and vascular components) is very important for the proper functioning of brain. Li et al. developed a model in rats for ‘enhanced neurovascular recovery’ and find that neural progenitor cell (NPC) transplantation therapy is not sufficient for treating the stroke but the combination of NCP and embryonic stem cell-derived vascular progenitor cells (VPCs) co-transplantation improved the functional recovery after stroke and might be better and effective therapeutic strategy for the treatment of stroke (Li et al., 2014).

**Stroke Rehab Device**

Rehabilitation is very important for stroke patients and should start immediately after treatment in hospitals. It is an organized effort of caretakers to help stroke patients to provide maximize all opportunities for returning to an active and productive lifestyle (Panel et al., 1997). In stroke patients the repetitive facilitation exercise (RFE) is one of the most common rehabilitation tactics exercise wrist exercises. Georgia Tech researchers have created a mechanical device in which pneumatic actuator tendon hammer hits a person’s wrist while a transcranial magnetic stimulator creates a weak signal in the brain’s motor cortex. The responses overlap in the brain, produce and send a strong signal back to the arm, and the wrist moves (Davies, 2005).

**Medtronic CoreValve® System**

Approximately 300,000 people worldwide suffer from severe aortic stenosis, and not eligible for open heart surgery because of high risk. The 471 patients were treated with novel self-expanding device, (Medtronic CoreValve® System, 2018). Patients were monitored by independent core labs and evaluated against a performance goal. This study was in partnership with the U.S. Food and Drug Administration. CoreValve Trial’s results for extreme risk patients were reviewed by FDA and after reviewing FDA have approved this device (not approved for commercial use in U.S.) (Anon, 2018; Medtronic, 2018).

**CONCLUSION**

Stroke is a complex pathophysiological process which caused by excitotoxicity, oxidative and nitrosative stress, peri-infarct depolarizations, inflammation as well as apoptosis. It is very frustrating to think scientists were involved over last two to three decades in research, even no full prove neuroprotective drug or mechanism is available.
to treat stroke. Patients suffer in unavailability of better treatment techniques, which can be easily provided in this science era. The present review demonstrates the known causal pathways of neurotoxicity/stroke as well as neuroprotective effect of astrocytes against different pathological reactions and inflammations with their treatment strategies. There are many researches recognizes the stroke and its causing pathway in initial stages and the treatment is done by treating the single causing pathway but not whole stroke symptoms. Recently researchers focused on therapies to protect at molecular level as well as rehabilitation. Aspirin is used in stroke against the thrombic clot but the life-threatening or major bleeding is also increased. For patients with stroke, only one FDA (Food and drug application) approved drug for stroke, intravenous tissue plasminogen activator (tPA), within 3 h or aspirin within 48 h of stroke onset, are interventions of proven benefits. Along this several other interventions and new technologies such as stroke detector microwave helmet, rehabilitation techniques, speech therapy, and physiotherapy are being used. Rather than this it is great demand to established new techniques to develop by researchers.

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