A Review on the Causes of Stroke and Remedy to Avert Stroke

Sugasri Sureshkumar [1*], K. Yogarajan [2]

[1] Head of the Department of neurology, Faculty of Physiotherapy,
Meenakshi Academy of Higher Education and Research, Chennai, India
[2] Associate Professor, National Institute for Empowerment of Persons with Multiple Disabilities (Divyangjan),
Kovalam, Tamil Nadu, India

Abstract

The article is important as the article has not only discussed the causes of "ischemic stroke and haemorrhagic strokes" yet it has also discussed causes related to cardioembolic stroke, cryptogenic stroke and others within the scope of this article. The findings show that the presence of different types of diseases and medical conditions such as "Sickle cell disease", "Chagas disease", "hypertension, diabetes and others are underlying causes of stroke within the individuals. In case these diseases have been controlled then it will lead to control over strokes. The findings also illustrate that oral coagulation will not provide desired results as per averting strokes while t-PA thrombolysis has fetched positive results.

Keywords

Stroke, Ischemic stroke, Haemorrhagic stroke, atrial fibrillation, hypertension and others.

INTRODUCTION

The article will discuss stroke which is widely prevalent and occurs among most people in different countries. Specifically, the article will point out the different causes associated with stroke to make the readers accustomed to those causes and the brain attack. Conversely, the article will also discuss the remedies that have been prevalent to avert the attack. The article will conduct a review on this topic from different journal articles. The article aims to conduct a review of the different causes and remedies for stroke. There are around 91 patients who have been diagnosed with recurrent strokes whereas 85.7% have been unaware of the essential symptoms of stroke [1]. Stroke has been the leading reason for death and also functional impairment.

Kerala has been considered to be a state with an increasing literacy rate where around 87.5% of the population have been seen to be unaware of the symptoms of stroke which has further resulted in an increasing number of morbidity and also mortality [2]. Therefore, it is proved that stroke is one of the diseases that people have been unaware of. India is a country where the occurrence rate of stroke within the young population has been higher in comparison with Western population. However, brain stroke has always been a matter of concern among the elderly population. The young population has been impacted by "*depression*", "*physical disability*", "*cognitive impairment*" and others. 15-30% of the young population have been witnessed to be affected by stroke [2]. "*Hyperhomocysteinemia*" is considered to be an essential medical condition that causes an increase in homocysteine level within the blood as prevalent among people possessing deficiency in Vitamin b12.

According to hospital records in India, "*cerebral venous thrombosis*" (CVT) is a distinctive type of stroke that is common in the country. It has been further reported that 12 times the young population has been affected by CVT as compared with the Western population. There are around 16.3% of strokes witnessed among the younger population which is further estimated to be much higher around the world [3]. As per the reports of "Indian Stroke Association" there are around 1.8 million of the population in India are affected by strokes [3]. Stroke is a non-communicable disease however, it has evolved as a threatening disease in the country that has been reducing both morbidity and also mortality. People in India do not possess enough knowledge of the risk factors of stroke which is the reason that prevalence rate across the country has increased.

LITERATURE REVIEW

Pathophysiology of Stroke

Stroke can be described as a "*focal neurological deficit*" in the association of a sudden onset whose symptoms last for around 24 hours. It can be better defined as the neurological outburst that has been caused by impaired perfusion with the help of the blood vessels towards the brain. [4] opined that the neurovascular anatomy is required to be understood to further study the clinical manifestation of stroke. The blood flow within the brain is managed through internal carotids as well as vertebral arteries. Ischemic stroke has been caused by deficient blood and also through oxygen supply to the brain. However, the occurrence of hemorrhagic stroke has been caused by bleeding or leaky vessels. *Ischemic occlusions* contribute to around 85% associated casualties within stroke patients while Ischemic occlusion also generates both "*thrombotic and embolic conditions*" within the brain.
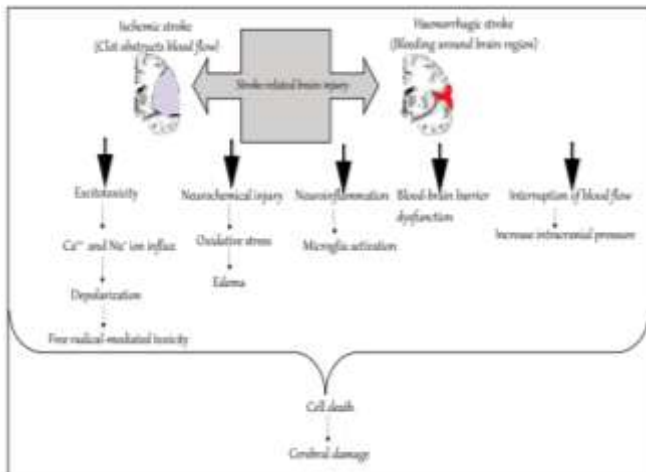
Figure 1. Molecular Mechanism associated with stroke (Source: [4])

Thrombosis is such a condition when the blood flow gets affected due to narrowing of the vessels in the wake of "*atherosclerosis*". In case of embolic stroke, the blood flow gets decreased within the region of the brain that causes "*embolism*". [4] argued embolism is such a condition when the blood flow eventually decreases in the brain and hence causes certain stresses as well as cell death named "*necrosis*". However, haemorrhagic stroke accounts for around 10–15% of strokes among individuals.

Ischemic stroke and Haemorrhagic stroke

Ischemic stroke takes place when the blood supply within the brain has been interrupted and reduced that has been causing a prevention in the brain tissue while receiving oxygen and also nutrients. [5] opined that "*neutrophil-to-lymphocyte ratio*" (NLR) has been correlated with the increased risk related to ischemic stroke. NLR is considered to be present within the peripheral blood reflecting certain balance among systemic inflammation and also immunity. The brain cells die within a few minutes in terms of occurrence of ischemic stroke. This type of stroke is due to blockage that eventually restricts the blood supply within the brain. Ischaemic strokes have been a consequence of "*cerebral small vessel disease*", "*large artery disease*" (atheroscleroisis) and also "*cardioembolism*". CSVD involves "*deep perforator arteriopathy*" as well as "*cerebral amyloid angiopathy*" (CAA).

"*Cardioembolic stroke*" is caused by cardioembolic disease (caused by atrial fibrillation) while large artery disease has been caused by ruptures within arteriosclerotic plaques that lead to formation of in situ thrombus. There are no specific causes found for cryptogenic stroke. Haemorrhagic stroke is a life-threatening condition that occurs when the blood vessels within the brain rupture and also bleed. [6] argued through the help of human data that plasma catecholamines and cortisol levels increase during the time of the onset of the stroke. Catecholamines are usually released within the blood where an individual is seen to be suffering from either physical or emotional stress whereas cortisol level indicates certain adrenal disorders. Haemorrhagic stroke can cause a disruption in the normal circulation of the blood within the brain that eventually starves certain areas from oxygen. The occurrence of haemorrhagic stroke is due to the weakening of the blood vessels.

Epidemiology and aetiology of stroke from global perspectives
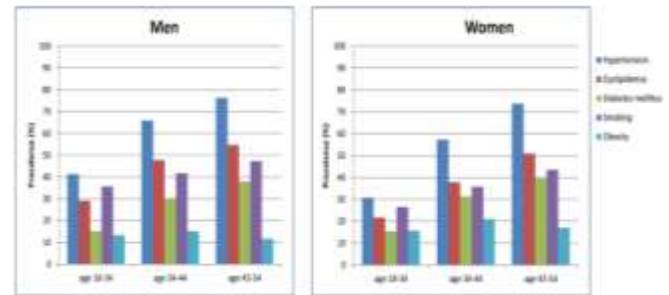

Figure 2. Prevalence of vascular risk factors within young patients categorised by age and also sex (Source: [7])

The stroke among the younger population has been found to be different where it has been reported that around "*5 to 15 per 100000 person-years*" within the European studies to around "*20 per 100000 person years*" within other countries such as Northern-American, Australian and

Asian studies and others. [7] stated that a maximum number of incidences have been found in low-income countries as compared with high-income countries. "*Sickle cell disease*" is considered to be a "*genetic haematological disorder*" that has been caused through "sickle mutation" upon those haemoglobin genes. There is an important form namely, "*homozygous haemoglobin S*" (HbSS) has an association with "ischaemic stroke". People with sickle cell disease have higher rates of "ischaemic stroke" that increases with age. The mild form is named "*heterozygous sickle cell trait*". "Sickle cell disease" has been assumed to be "monogenic disorder" accompanied by stroke, which is a primary manifestation.

The "*rheumatic heart disease*" is prevalent among ischaemic patients differs from around 1.8% to 2.0%. *Chagas disease* is assumed to be a "*parasitic disease*" and there are stroke incidences among patients possessing this parasitic disease. [8] argued that hypertension is witnessed among people encountering strokes and is considered to be a modifiable risk factor. For example, "*Preeclampsia*" is a relevant hypertensive disorder associated with pregnancy that eventually increases the stroke risk by around 4 to 5 folds in comparison with conditions of normal pregnancy. It is important to notice that the prevalence of ischemic stroke is much higher as compared with haemorrhagic stroke. It has been further found that there is a high risk of occurrence of this stroke with "*HIV*", "*tuberculosis*" and also "*neurocysticercosis*". "Neurocysticercosis" is a parasitic

disease that has been caused by tapeworm's cerebral cysts where patients with this disease encounter stroke.

Relevant causes of stroke

In case of ischaemic strokes, blood clots occur in different areas where some of the arteries have narrowed over time through *fatty deposits* and this process is termed *atherosclerosis*. The arteries may become narrower with age while possible causes are assumed to be smoking, obesity, high blood pressure, diabetes and others. The most important cause of ischaemic strokes is irregular heartbeat namely, *atrial fibrillation*. The irregular heartbeat may result in blood clots within the heart which eventually break apart and eventually end up within the blood vessels supplying the brain. [9] stated that the cases of "ischemic stroke" have been categorised into "*large artery atherosclerosis*" (LAA) (occurs in the head and also in the neck), "*small artery occlusion*" (SAO) (subcortical infarcts), "*stroke of undetermined cause*" (SUD) and others.

The relevant causes of *haemorrhagic stroke have been high blood pressure*, which w*eakens the arteries within the brain and eventually causes a rupture and split*. As the risk related to blood pressure increases, therefore, it causes *overweight, smoking, stress* and others. However, haemorrhagic stroke is assumed to have been caused by expansion of the blood vessels or through abnormal expansion of the vessels within the brain. The causes of strokes concerning the two categories have been identified to understand the causes associated with them. [10] argued that there are two types of haemorrhagic stroke that are intracerebral haemorrhage as well as subarachnoid haemorrhage. Intracerebral haemorrhage is caused by bleeding in the brain tissue whereas subarachnoid hemorrhage occurs due to bursting of blood vessels in the brain therefore, "*brain aneurysm*" (bulge) that occurs within the blood vessel that has been caused by weakness in those walls of vessels.
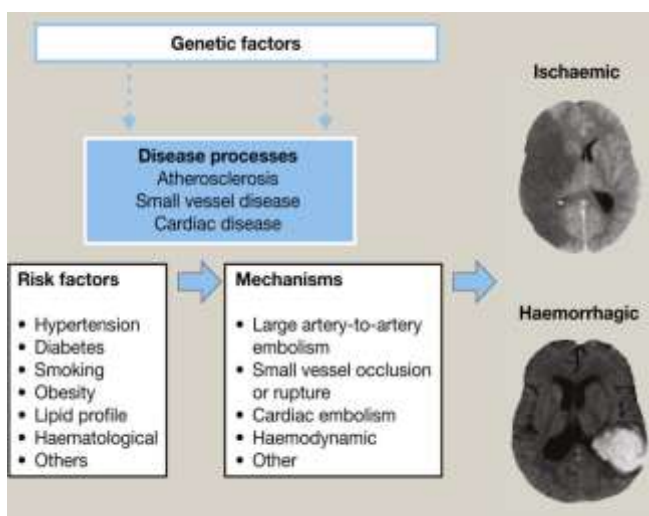
Figure 3. Identification of risk factors and mechanisms for Ischaemic and Haemorrhagic strokes
(Source: [11])

There are around *35% of young patients suffering from ischaemic stroke* therefore, hypertension is a risk factor. Diabetes Mellitus has been seen in people suffering from stroke which has been encountered within *10% of patients*. [11] opined that different prolonged diseases lead to occurrence of strokes. It has been seen that *50% to 60% of the patients* both men and women possess dyslipidaemia. *50% of the young patients* have reported that they are smokers while obesity as defined by "*Body Mass Index" (BMI)* is 30 or more than that have been witnessed among *10% of the individuals possessing stroke*. Air pollution is another pertinent cause of stroke where rapid growth of the economy may lead to transformation of air quality. The geographical differences are associated with stroke-associated mortality in the wake of air pollution.
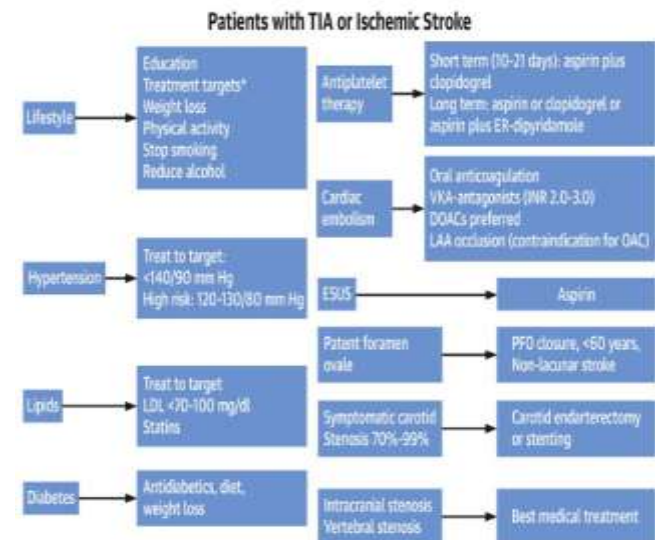
Remedy and Stroke treatment

Figure 4. Prevention of Stroke
(Source: [12])

The first stroke can be prevented followed by recurrence of the second stroke within an individual. Primary prevention in respect of "ischemic stroke" involves *modification of lifestyle* and *diet*. Treatment of the risk factors (diseases such as hypertension, diabetes mellitus and others) along with offering *antiplatelet therapy for those patients with high vascular risks* followed by *anticoagulation for atrial fibrillation*. However, secondary prevention includes stenting *in some symptomatic patients*, *carotid surgery*, *treatment for insulin resistance* and also best treatment in the form of "*intracranial stenosis*" [12]. The most eminent remedy for cerebral hemorrhage (Haemorrhagic stroke) revolves around treating "*hypertension*", "*occlusion with the left atrial appendage*", "*reduction in alcohol intake*", "*permanent contraindications for oral anticoagulation*" and others.

Additionally, anticoagulation treatment is found to be highly effective in reducing stroke risks within individuals who have been detected with atrial fibrillation [12]. The

challenging area is that in most the cases, patients possessing atrial fibrillation remain asymptomatic and thus this disease atrial fibrillation does not get diagnosed on time. In case risk factors have been addressed then it will lead to prevention of the strokes even before the occurrences of the strokes within individuals.

METHODOLOGY

Atrial Fibrillation has been detected through "***Continuous ECG Monitoring Using Implantable Loop Recorder***" which will help in prevention of strokes within people with high risks. A randomised controlled trial (RCT) has been conducted where the eligible participants have been assumed to be between 70-90 years and have been eventually diagnosed with one out of the four conditions such as "***hypertension***", "***heart failure***", "***diabetes***", and others. There is another important condition that has been considered where these patients have not encountered atrial

Fibrillation in the past. The patients have never been implemented with pacemaker, neither have consumed anticoagulation medicine nor have encountered contraindication towards anticoagulation. The inclusion criteria for including these patients have been considered through RCT. The ***12-lead ECG*** has been considered for evaluating atrial fibrillation [13]. The trial has been designed as well as overseen with the help of the steering committee.

The participants have been randomly assigned in a ratio of 1:3 to two different groups that are an "***implantable loop recorder***" (ILR) group and also a controlled group. The online system has been utilised for conducting this study on these groups. There are around 4 to 8 participants who have been stratified. Therefore, it is clear that stratified sampling techniques have been adopted for the study. ***Stratified sampling technique*** is about division of the population into different subpopulations based on various characteristics including age, income, job role and others [14]. The eligible participants have been assigned to certain nurses who have been considered only after enrollment. Thus, the participants have fair knowledge in understanding of the causes of the strokes due to atrial fibrillation as these nurses have been attending to the patients who have been suffering from strokes according to age groups. The baseline assessment has prioritised receiving the details related to medical history, assessment of vital signs, blood samples and others. Both the blood pressure and also the pulse rates of the participants have been recorded followed by supine rest that contains the automated measurements
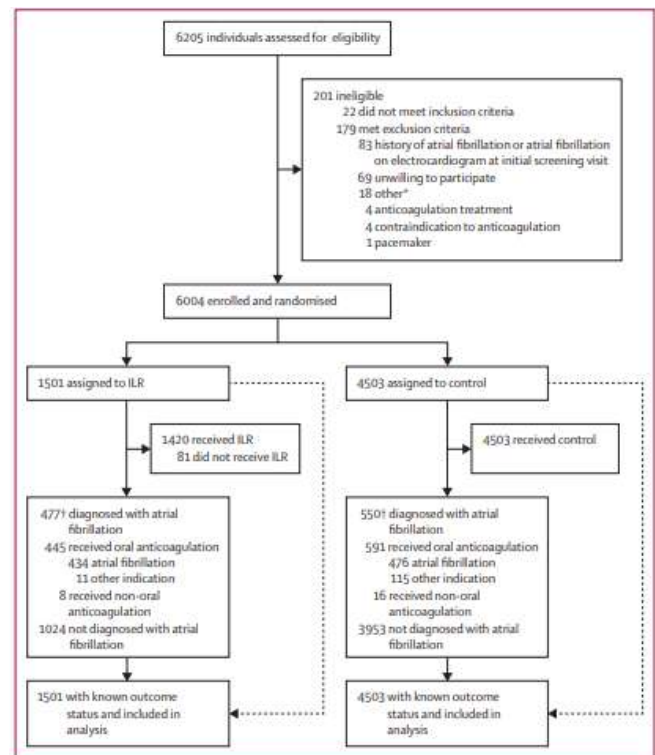

Figure 5. Trial Profile
(Source: [14])

ILR implantation has been planned within 4 weeks where ECG has been monitored in respect of every patient. In case atrial fibrillation has been found to have lasted for around 6 min then that participant has been recommended with oral anticoagulation [14]. The option for deciding on anticoagulation along with the clinical tests has been given to the physicians and also to the patients. The primary outcome has been a combination of "endpoint of stroke" or rather "systemic arterial embolism" whereas the secondary outcome has been revolving around "combined endpoint of ischaemic stroke", "systemic arterial embolism", or "cardiovascular death" and others. The remaining results are important and include "initiation of anticoagulation", "***Thrombosis***", "***Haemostasis***" and also "***haemorrhagic stroke***". The episodes associated with "***new onset ILR-detected atrial fibrillation***" have lasted for around 6 minutes that would be adjudicated by two cardiologists. The assumption that has been made before sample size is "***1·00 per 100 person-years***" within the control group while "***0·65 per 100 person-years***" within the ILR group.

FINDINGS AND DISCUSSION

Findings

The result shows that around ***6205 individuals*** have been screened and around ***6004 are included***. The exclusion criteria are that participants diagnosed with atrial fibrillation in the past have been excluded during the initial stage when those participants have been screened through the ECG. ***1501 have been assigned within the ILR group*** while around ***4503***

have been assigned within the control group as per the sample size. The mean age of those participants has been estimated to be around 74·7 years while 2837 are women. There have been around *1420 participants who have been engaged in receiving ILR* within the ILR group whereas the period considered for implantation has been around 24 days. However, there have been no participants who have been involved from the control group. Atrial fibrillation has been diagnosed among *477 out of those 1501 participants* within that ILR group while around *550 participants out of 4503 from the control group* have been diagnosed with the same disease [14].

Further results show that *426 participants out of those 477 participants* have been diagnosed with atrial fibrillation within 3 years. Therefore, the number of participants tending atrial fibrillation has increased in 3 years [14]. Oral anticoagulation has been provided to 445 patients within those ILR groups while around *591 within the control group*. 375 participants possessing atrial fibrillation who have been initiated with oral anticoagulation in the first month only after its diagnosis followed by 434 at every time as per the requirement.

Additionally, within the control group, there are almost *393 participants who have been initiated with oral anticoagulation* suffering from atrial fibrillation after its diagnosis. There has been a discontinuation of oral anticoagulation when *42 patients have been confirmed to possess atrial fibrillation in the ILR group* while *17 participants from the control group* also discontinued oral anticoagulation [14]. The stroke has occurred among 318 participants within the ILR group while 251 participants in that control group have encountered stroke. Cardiovascular death has also been seen to have occurred among 43 participants in the ILR group and 157 participants in the control group.

The results of the administration of thrombolysis have been revolving around found in the aftermath of ischemia onset. Thrombin injections have led to occlusion towards the "*middle cerebral artery*" (MCA) (a different type of stroke). There has been an observation time that has been assumed to be around 2 hours where complete recanalisation has been seen to be attained t-PA within treated mice. There has been no clot dissolution seen within those mice while partial recanalisation has been found to have occurred. It has been further found that t-PA treatment has resulted in an increase of reperfusion level that becomes around "*61% ± 4.9%*" in comparison with around "*44% ± 3.5%*" as well as "*71% ± 7.9%*" that has been compared with "*47% ± 2.7%*" within the "penumbra". There has been a reduction of red blood cells accompanied by "vasoconstriction" [15]. "*Neutrophils stalling capillaries*" have contributed towards "*no-reflow phenomenon*" where the application of "*monoclonal anti-Ly6G antibody*" has resulted in depleting "*neutrophils*". There have been capillary stall points and also penumbra that has been diagnosed among those mice after the occurrence of the stroke.

Discussion

Adoption of STROKESTOP trial

The participants tending occurrence of strokes have been provided with anticoagulation has not resulted in reducing the stroke risks. The result has somehow proved that high acceptance of anticoagulation therapy has been wrong in providing treatment to patients with a tendency to stroke risks. The screening strategy has been witnessed to help detect the disease among the patients followed by adoption of an intervention that will eventually reduce the risks of strokes among those participants who already tend to the risks for strokes. *STROKESTOP trial* has been utilised as the screening method which has provided effective results as there is a reduction of "ischaemic stroke", "haemorrhagic stroke", "systemic embolism" and others [14].

In terms of random selection, there is one aspect that has been prioritised where it has been seen that those participants always have hypertension which has led to stroke risks. The primary outcome has fetched results as there has been a reduction of around 35% among people with stroke risks [14]. The risk reduction after initiating oral coagulation is 20% where around 91% of the participants have been witnessed to be provided with oral coagulation. There is a minimal reduction in stroke occurrences among those participants. Therefore, remedy in the form of oral coagulation will not be helpful for patients having high risks of stroke and thus, there is a requirement for an enhanced remedy as found in the above results. Oral anticoagulants have previously been thought as effective to prevent unwanted clots of blood.

Thrombin Model of Stroke

The "distal capillary flow" has been measured through recanalisation within the mice encountering strokes for identification of underlying mechanisms within no-reflow phenomenon. The "*Thrombin Model of Stroke*" where has been illustrated that "cortical perfusion" has been monitored through utilisation of "*laser speckle contrast imaging*" (LSI) at the time of the onset of the stroke [15]. The treatment with the help of "anti-Ly6G antibody" and "t-PA thrombolysis" have fetched certain positive outcomes where the results have shown an increase in tissue reperfusion which indicates a link among "*capillary stall and no-reflow*" [15]. RBC velocity has enhanced the distal branches within the MCA. Simultaneously, there has been reduction in the damage of the ischemic tissue after the stroke occurrences within the mice after around 7 days.

Every animal that has been treated through t-PA has eventually shown evidence in the form of "*hemorrhagic infarct transformation*" within the brains of the mice. The systematic effect of antibody as per evaluating the severity of the stroke without the utilisation of the "thrombolysis" shows an enhancement within the "*cerebral blood flow*" and also provides a neurological outcome. The "*no-reflow of brain microvascular networks*" has always been popular since

1968. Multiple mechanisms have contributed towards the "*microvascular no-reflow phenomenon*". Clinical studies in recent times have provided certain evidence in the form of elevation in the "blood neutrophil count" that has been administered as a biomarker that has provided an unfavorable outcome within stroke patients who have been getting thrombolysis. Neutrophil depletion provides facilitation in terms of recovering from stroke through facilitating capillary reperfusion.
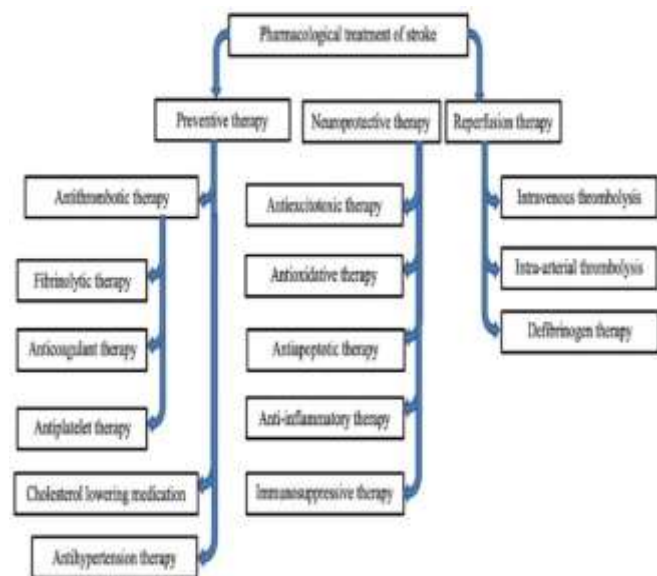
Research on Drugs

Figure 6. Pharmacological treatment for stroke
(Source: [16])

Minimilisation of the neuronal cell damage and also death that has been triggered through ischemia and also metabolic cascade have been caused through abrupt reperfusion. The treatment involves retardation and rehabilitation of the progress of the vascular disease for preventing additional strokes. The pharmacological agents can be utilised for treating the stroke whereas on the other hand, insufficient levels of oxygen cause energy deprivation while "*arterial thromboembolic episode*" is considered to be ischemic cascade [16]. The current trails before "acute ischemic stroke" aims at liberating and reinstating the ischemic penumbra for the particular treatment rather "*energy abrogation*" which will cause a deterioration in ion homeostasis and will trigger certain increase within the extracellular concentration of the potassium ions while a reduction within the chloride and sodium ions.

Thrombolysis revolves around pharmacological drugs causing a breakdown of blood clots to enhance blood flow. Thrombotic drugs have already gone through human trials and it has begun around 1960s and 1970s. The drugs have been helpful for clot formation and have provided results of faster recovery in the aftermath of strokes. rtPA has been administered through infusion where the resultant PAI-1 levels are not liable for controlling tPA action that has been

causing the body to possess insufficient quantities to break the fibrin clots [17]. Food and Drug Administration (FDA) has already approved alteplase-rtPA thrombotic for averting the risks of stroke. An effective drug contains the combination of "rtPA", "p-anisolylated", "urokinase" and others.

Intravenous Thrombolysis (IVT) is assumed to be a primary treatment for patients who have encountered ischemic stroke. IVT in association with alteplase has provided clinical results and has revived inflammatory response within patients suffering from cerebral ischemia [18]. Conversely, Mechanical thrombectomy is appropriate for patients possessing acute cases related to ischemic stroke as it includes large arterial occlusion along with anterior circulation. "*IAT Intra-Arterial Thrombolysis Therapy*" is about administering several agents in the artery for dissolving thrombosis however, "plasminogen activators" have been used in respect of "intra-arterial thrombolysis".

CONCLUSION

The article has discussed the different types of strokes and its causes especially ischemic and haemorrhagic strokes. There is a neurological deficit that has been caused due to stroke which is the most important definition of stroke as discussed in this article. Both the type of strokes somehow causes a disruption in the blood supply and blood circulations in the human body. Carotid surgery, antiplatelet therapy and others have been assumed to be some relevant methods to abstain from the occurrences of the onset of strokes. Health condition such as diabetes, hypertension and others are required to be controlled to avert the onset of stroke.

REFERENCES

[1] India, P.T.of (2022) *More than 85% of stroke patients unaware of symptoms: Survey, NDTV.com. NDTV.* Available at: https://www.ndtv.com/india-news/more-than-85-of-stroke-patients-unaware-of-symptoms-survey-3471152 (Accessed: December 27, 2022).

[2] *www.ETHealthworld.com (2022) Brain stroke commonly occurring in young Indian population, Health News, et Healthworld, ETHealthworld.com.* Available at: https://health.economictimes.indiatimes.com/news/diagnostics/brain-stroke-commonly-occurring-in-young-indian-population/95164906 (Accessed: December 27, 2022).

[3] *Stroke, one of the leading causes of death and disability in India requires a comprehensive solution (2020) Hindustan Times.* Available at: https://www.hindustantimes.com/brand-post/stroke-one-of-the-leading-causes-of-death-and-disability-in-india-requires-a-comprehensive-solution/story-PMVKkmgIbNlYt2pRGyphiO.html (Accessed: December 27, 2022).

[4] D. Kuriakose and Z. Xiao. Pathophysiology and treatment of stroke: present status and future perspectives. *International journal of molecular sciences*, 21(20), p.7609, 2020.

[5] S.Y. Song, X.X. Zhao, G. Rajah, C. Hua, R.J. Kang, Y.P. Han, Y.C. Ding and R. Meng. Clinical significance of baseline neutrophil-to-lymphocyte ratio in patients with

ischemic stroke or hemorrhagic stroke: an updated meta-analysis. *Frontiers in neurology*, *10*, p.1032, 2019.

[6] A.R. Saand, F. Yu, J. Chen and S.H. Chou. Systemic inflammation in hemorrhagic strokes–A novel neurological sign and therapeutic target?. *Journal of Cerebral Blood Flow & Metabolism*, *39*(6), pp.959-988, 2019.

[7] E. Boot, M.S. Ekker, J. Putaala, S. Kittner, F.E. De Leeuw and A.M. Tuladhar. Ischaemic stroke in young adults: a global perspective. *Journal of Neurology, Neurosurgery & Psychiatry*, *91*(4), pp.411-417, 2020.

[8] M.J. Cipolla, D.S. Liebeskind and S.L. Chan. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. *Journal of Cerebral Blood Flow & Metabolism*, *38*(12), pp.2129-2149, 2018.

[9] W. Wei, S. Li, F. San, S. Zhang, Q. Shen, J. Guo and L. Zhang. Retrospective analysis of prognosis and risk factors of patients with stroke by TOAST. *Medicine*, *97*(15), 2018.

[10] M. Wajngarten and G.S. Silva. Hypertension and stroke: update on treatment. *European Cardiology Review*, *14*(2), p.111, 2019.

[11] S.J. Murphy, and D.J., Werring. Stroke: causes and clinical features. *Medicine*, *48*(9), pp.561-566, 2020.

[12] H.C. Diener, and, G.J. Hankey. Primary and secondary prevention of ischemic stroke and cerebral hemorrhage: JACC focus seminar. *Journal of the American College of Cardiology*, *75*(15), pp.1804-1818, 2020.

[13] J.H. Svendsen, S.Z. Diederichsen, S. Højberg, D.W. Krieger, C. Graff, C. Kronborg, M.S., Olesen, J.B. Nielsen, A.G. Holst, A. Brandes, and K.J. Haugan. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *The Lancet*, *398*(10310), pp.1507-1516, 2021.

[14] H.K., Mohajan. Qualitative research methodology in social sciences and related subjects. *Journal of Economic Development, Environment and People*, *7*(1), pp.23-48, 2018.

[15] M. El Amki, C. Glück, N. Binder, W. Middleham, M.T. Wyss, T. Weiss, H. Meister, A. Luft, M. Weller, B. Weber and S. Wegene. Neutrophils obstructing brain capillaries are a major cause of no-reflow in ischemic stroke. *Cell Reports*, *33*(2), p.108260, 2020.

[16] D. Frank, A. Zlotnik, M. Boyko, and B.F. Gruenbaum. The Development of Novel Drug Treatments for Stroke Patients: A Review. *International Journal of Molecular Sciences*, *23*(10), p.5796, 2022.

[17] G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.H. Cho, F. Fazekas, J. Fiehler and I., Ford. MRI-guided thrombolysis for stroke with unknown time of onset. *New England Journal of Medicine*, *379*(7), pp.611-622, 2018.

[18] B. Keselman, C. Cooray, G. Vanhooren, P. Bassi, D. Consoli, P. Nichelli, A. Peeters, D., Zini, A. Sanak, N. Wahlgren, and N. Ahmed. Intravenous thrombolysis in stroke mimics: results from the SITS International Stroke Thrombolysis Register. *European journal of neurology*, *26*(8), pp.1091-1097, 2019 .