Three different routes on treating the ischemic stroke

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Abstract: There are many possible factors could finally lead to stroke which has a crucial influence on people 'communication and brain function. People with diabetes, obesity, heart diseases and hypertension is in a risk of stroke[1]. Stroke is one of the most common diseases of elders and has a high incidence in the modern cities. Failure in delivering oxygen and nutrients to brain tissues, generating a irreversible damage. The number of cellular death is proportional to the time from stroke happen. Once the 'ischemic core' consists of tissue that receivers cerebral blood flow less than10mL/100g per minute, the majority of cell starting to apoptosis in couple minutes. [2]Reasons of causing the ischemic stroke mainly consist of atherothrombosis, cardiogenic embolism and Small Vessel Disease. The incidence of atherothrombosis could increase as a result of having diseases like diabetes, hypertension, hypercholesterolemia, hyperfibrinogenemia and hypergammaglobulinemia. Those diseases could change the blood flow by lowering the shear stress. In that cause, once the blood has lower shear stress and flows slow as usual, it will causes rising up of the blood viscosity.[3] Blood with higher viscosity is tend to coagulate in narrow sites of the vessel and blot the vessel. Hence, oxygen or other nutrients can not transfers as planned and leads to brain damage. In past ten years, due to a stronger intervention of atherothrombosis from the society, the incidence of cardiogenic stroke has been rising. The atrial fibrillation (AF) is one of the most common type of cardiogenic disease.[4] Its incidence is aged-associated .The elders are in a higher risk compared to the youth. Study has showed that non-AF associated stroke causes less than a half fatality rate. Furthermore, ischemic stroke related to AF is predisposed to recur more frequently and impacts a severe deficits of human function.[5] The initial symptom of AF is usually difficult to diagnose, thus the prevention of AF is normally be insufficient. The third essential reason of causing in the ischemic stroke is Small Vessel Disease (SVD).Cerebral Small Vessel Disease was found that has a great connection of ischemic or haemorrhagic stroke.[6]. Therapies against ischemic stroke existed today could majorcharacterized by Antiplatelet, Anticoagulation and Thrombolysis. The aim of this study is to review various routes to treat ischemic stroke.

1. Platelet

Platelets which produced by megakaryocytes play a crucial part in the vessel. After the formation from megakaryocytes, platelets could exist in vessel for 5-7 days. They are known for their ability to manipulate the hemostasis and thrombosis. Platelets would generate quickly to produce occlusive blots to stop the haemorrhage in pathological conditions. Platelets are biophysical nature of the blood component, as a result of that, they flow closely to the vessel wall. It has been shown that platelet responses quickly when vessels under attacked due to its proximity to vessel wall. [7] Once the vessels being insult or getting injury, Vascular endothelial tissue will activate the release, adhesion and coagulation of platelets. As a result of that, it will causes hemostasis and blood clot. When the platelets are in an active state, they generate their ability of supporting the formation of thrombin and acceleration of coagulation. [8]Hence, many drugs have been designed to target at platelets to prevent the production of arterial thrombus. Aspirin, clopidogrel and Aggrenox are commonly used on the market.

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2. Antiplatelet

Recent studies have presented that antiplatelet is a safety and efficient route to handle ischemic stroke by restraining the activation of pathways of platelets and consequently leads to less formation of blood clots. Antiplatelet process focuses on different clot etiology and finally changes various intrinsic pathways compared to anticoagulant process. Among the routes of antiplatelets, they are various as well. To be more precise, While aspirin inhibits TXA2 formation, clopidogrel and prasugrel inhibit the P2Y12 (ADP) receptor and dipyridamole inhibits phosphodiesterase. Oral anticoagulants also inhibit the normal function of different embolism factors such as factors II,VII,IX, and X.[8]. Many clinical studies show that anticoagulants have a relatively great impact on prevention of noncardioembolic and cardioembolic stroke.

3. Mechanism of antiplatelet drug

3.1. Aspirin

Aspirin is a typical drug which was commonly used in antiplatelet therapy. It has a short half-life that less than 3 hours. Aspirin initially acetylates the receptors of enzyme COX1 then makes it activated. Once the enzyme COX1 is in active state, it would restrain the process of arachidonic converting into prostaglandin endoperoxides and transient intermediates for formation of TXA2. Regardless of the essential role that TXA2 plays in platelet aggregation and vasoconstriction, aspirin can still inhibit primary hemostasis. [8]In many clinical trials, more and more evidences have indicated that excess bleeding is the most critical harm connected to the aspirin use, and its risk and fatality rate are proportional to age. People in higher age are at a higher risk of it. On the top op that, using aspirin also results in gastrointestinal (GI) bleeding, and peptic ulcer; Physician should balance the benefits against the harms before administrate aspirin to patients. [9]

3.2. Clopidogrel

Clopidogrel shows a totally different action mode than aspirin. Clopidogrel has no function on antiplatelet therapy before convert into its active state, it means clopidogrel is a prodrug. It is inactive until it is hydrolysed by cytochrome P450 in the liver vis an nicotinamide adenine dinucleotide phosphate (NADPH)-dependent mechanism. After it becomes active, it would bind irreversibly to ADP receptor that located on the membrane of platelets which called P2Y12.Under this situation, it will attenuate the possibility of ADP binding to platelets, hence restraining platelet activation and subsequent thrombus generation. [8]

4. Coagulation

As we know, blood is a liquid that would transfers through the whole body under the pressure of vasculature. This process is circulation of blood. Blood would immediately converts into gel(‘clot’) to plug the hole, when the vessel gets cut or injury, and minimize further blood loss. The plasma portion of blood contains proteins that work together in a activating enzyme associated with cascade. The mechanism of how blood clotting cascade get initiated consists of two main routes, one is hemostasis, the other one is pathologic thrombosis. Hemostasis is the common process by which the clotting cascade seals up vascular damage to reduce blood loss after getting injury. Two major pathways exist for triggering the blood clotting cascade, known as the tissue factor pathway and the contact pathway.[10]

5. Tissue factor(extrinsic) pathway

The plasma clotting cascade consists of an array of reactions associated with initiation of zymogens with the help of limited proteolysis. Serine proteases would be catalytically activated by the resulting enzymes, but at this time, the enzymes don’t have intrinsic impact as isolated proteins

until binding to protein cofactor on particular membrane site. The enzyme activity become five time stronger that it used to be. The protein cofactors of the blood clotting cascade also literally circulate in the plasma as inert procofactors that must be converted into active cofactors via limited proteolysis. There are two subunits of enzyme by which the TF pathway triggers. the catalytic subunit is the trypsin-like serine protease, fVIIa, and the positively-acting regulatory subunit ("protein cofactor") is the cell-surface protein. [10]

6. The contact pathway

The contact pathway of coagulation is initiated when factor XII (fXII) is activated. This process also have a big deal with high-molecular-weight kininogen(HK) and plasma prekallikrein(PK) . Connection between blood and artificial surface is the essential character that change the fXII conformation and subsequent resulting in the formation of small amounts of active factor XII (fXII). Further reciprocal activation of fXII by kallikrein, and PK by fXIIa, results in a positive feedback loop. The conversion of fXI to fXIa is triggered by the upstream of fXI being active. Limited proteolysis of fIX to fIXa by fXIa then allows for formation of the "intrinsic tenase" complex. The final common pathway of blood clotting resulting in thrombin formation and blood clot. [10]

7. Anticoagulation

Date back to the early history, Vitamin K antagonists, Warfarin, were the only anticoagulants commonly and widely used in the market. it shows a great therapeutic function in anticoagulant then popular accepted by physician until it has been reported more than 65,000 patients are treated in U.S. emergency departments(ED) annually for warfarin-associated haemorrhage. High rate of bleeding along with the narrow therapeutic index of warfarin and need for frequent blood concentration monitoring, generated people to create a safer and convenient control anticoagulants without frequent and strict monitoring. Up until now, there have been several novel anticoagulants (NACs) created, including direct thrombin inhibitors (e.g.dabigatran), and factor Xa inhibitors (e.g. rivaroxaban, apixaban), designed to generate a safer anticoagulation compared to Warfarin. Those drugs target various site of the coagulation cascade which this review would discuss below.

8. Warfarin

Warfarin is highly water soluble, is rapidly absorbed from the gastrointestinal tract, has high bioavailability belongs to Vitamin K antagonist (VKAs), function by blocking the Vitamin K-epoxide reductase, subsequently lowering the rate of generating the vitamin K-dependent clotting factors. [11][12]The exact process is initially restrain the coagulation factors II, VII, IX, and X to interfere the conventional ability of proteins C and S, then followed by a delayed antithrombotic effect. Although the anticoagulant effect of VKAs is occupying the main position, a transient procoagulant effect may be generated when baseline protein C and protein S levels are reduced due to the initiation of VKA therapy and the acute phase of a thrombotic event and before the balanced decrease of vitamin K-dependent clotting factor levels is achieved. [13, 14]

9. Dabigatran(Direct thrombin inhibitor)

Dabigatran is a direct thrombin inhibitor (DTIs). As its name implies, the DTIs inhibit the intrinsic activity of thrombin. [15]Compared to heparin, it does not require any factor, and can inhibit thrombin directly. For now, most direct thrombin inhibitors are administered parenterally, such as argatroban, bivalirudin; Whereas dabigatran is orally administered which is easier to administer and have a better patient compliance. Due to this point, mang physician consider it is up-and-coming. These drugs are used for prophylaxis and treatment of VTE and ACS, and for prophylaxis of thrombus formation in non-valvular atrial fibrillation. [14]

10. Rivaroxaban(Factor Xa inhibitors)

Factor Xa inhibitors are used for prophylaxis and therapy of VTE, as well as for prophylaxis of embolic disease in non-valvular atrial fibrillation. These drugs target in Xa and generate inhibition which is the first step of the common pathway, either directly or indirectly. The inhibition level is proportional to dose. [16]These drugs bind directly to active site of factor Xa and consequently elicit the inhibition against both free and clot-associated factor Xa. They also inhibit prothrombinase activity to generate a conformational change, thereby inhibiting factor without having effect on IIa. Then finally leads to less formation of thrombin. [14, 17]And Apixaban and Edoxaban sharing a similar mechanism with Rivaroxaban. Adverse reactions associated with Xa inhibitors include hemorrhage and thrombocytopenia. Hemorrhage is a common side effect like all the other anticoagulants.[17]Whereas, the mechanism of causing the thrombocytopenia is unclear. No reversal agent has been found yet, both rVIIa and PCC have been proposed.[18,19]

11. Fibrinogen

Fibrinogen is inactive until converts into fibrin, the primary protein component of a blood clot, produced in liver. Hence, patients with liver disease may probably at a higher risk on ischemic stroke. [20, 21] Fibrinogen activated by either tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA) promotes fibrin breakdown. Whereas t-PA is synthesized and released by endothelial cells, u-PA generated by monocytes, macrophages, and urinary epithelium. u-PA and t-PA are cleared by the liver after performs their function . [22]Prothrombin activator plays an essential role on this activated Process .Fibrin shows a great connection with hemostasis as being both the primary product of the coagulation cascade and final substrate for fibrinolysis. The efficiency of fibrinolysis is controlled by multiple factors, includes fibrinogen isoforms, polymorphisms and clot structure, the amount of thrombin formation and cells associated with thrombus such as platelets. [22]Once fibrin clot is accumulated, it may lead to a variety of pathological disorders including storke or inflammation. [23]

12. Fibrinolysis

Fibrinolytic process is a co-operative job done by a wide array of cofactors, receptors, and inhibitors. Fibrinolytic activity can targets either on the surface of a thrombus containing fibrin, or profibrinolytic receptors on the cells. Many clinical trials have indicated acquired and congenital lack of profibrinolytic receptors contribute to disease morbidity, and new essays have found fibrinolysis having effect on multiple clinical settings. Since 1995, intravenous recombinant tissue plasminogen activator(rt-PA) therapy (IVT) has been indicated to have a great influence in treating the Acute ischemic stroke which is one of the leading causes of death and disability in the world.[24]Intravenous administration of rt-PA provide benefit after 3 to 4.5 hours of symptom onset. Due to various factors like clot size, site, and composition, with larger, proximal, and more fibrin-rich clots being resistant to thrombolytic therapy, patients administrated with rt-PA show variable outcomes. [25]

13. Conclusion

Stroke is a sudden loss of brain function caused by partially blocked blood supply to central nervous system. It does a harmful damage to human body because it leads to death of nerve cell that would never rebirth again. The number of nerve cell is limited and fixed, hence, brain function would not recover to what it used to be after having stroke. Neuro system protection after having stroke to which has not been paid enough attention. The blood-brain barrier (BBB), as we known, plays an essential role in regulating transfer of fluid, solutes and cells at the blood -brain interface and maintaining the homeostatic microenvironment of CNS. Under pathological conditions, such as ischemic stroke, the normal function of BBB can be interfered [26, 27], followed by the

extravasation of blood components into the brain and weaken neuronal function.[28,29]In that case, in my opinion, we should focus more on the nerve protection after ischemic stroke because of its seriousness towards the human health. Beyond field that physician, pharmaceutical chemist, and biologist can make effort to, normal people could also do a lot to prevent the stroke. Observational date indicate that having a heathier lifestyle resulting in a less risk of having stroke. Modifications of heathy diet(intake less salt, sugar), eliminating smoking, reducing alcohol consumption, having a regular physical exercise, achievement of normal body weight and treatment of hypertension are beneficial for stroke prevention.[29,31]

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