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Review

Is the Cerebral Intra-Arterial Heparin Flushing (IAHF), Beneficial for the Treatment of Ischemic Stroke?

Moh Hasan Machfoed[1*], Achmad Firdaus Sani[1], Amiruddin Aliah[2], Abdul Muis[2], Susi Aulina[2], Andi Kurnia Bintang[2], Ashari Bahar[2], Jumraini[2], Mohammad Kurniawan[3], Fenny L Yudiarto[4] and Fritz Sumantri Usman[5]

[1]Department of Neurology, Medical Faculty of Airlangga University, Dr Soetomo Hospital, Surabaya, Indonesia.

[2]Department of Neurology, Medical Faculty of Hasanuddin University, Dr Wahidin Soediro Husodo Hospital, Makassar, Indonesia.

[3]Department of Neurology Medical Faculty of University of Indonesia, Dr Cipto Mangoenkusumo Hospital, Jakarta, Indonesia.

[4]Department of Neurology, Medical Faculty of Diponegoro University, Dr. Kariadi Hospital, Semarang, Indonesia.

[5]Department of Neurology, Fatmawati Hospital, Jakarta, Indonesia.

Abstract

Since 2012 until now, in Indonesia, there has been an interventional medical procedure that is called brain washing. Without preceded by an in-depth study, this procedure has been applied to the community. The purpose of this procedure is to treat, both acute and chronic ischemic stroke.

In 2013, the American Heart Association (AHA)/American Stroke Association (ASA), published a Guideline for the Early Management of Patients with Acute Ischemic Stroke. The managements consist of the use of recombinant tissue plasminogen activator (rtPA), endovascular treatment, including intra-arterial fibrinolysis, mechanical clot retrieval, acute angioplasty and stenting.

Unlike acute ischemic stroke, until now, no guidelines have been provided about the management of chronic ischemic stroke that approved universally. Many studies were conducted in various ways, but no evidence based studies have been approved yet. Among them are the uses of medical rehabilitation, stem cells and others.

The purpose of this article is to review the brain washing procedure, in accordance with the applied scientific principles and is based on the standard literatures and guidelines.

Keywords: IAHF; CBF; Ischemic Stroke

Introduction

Stroke is a major cause of mortality and disability worldwide [1]. According to the data of Riskesdas, stroke is the first rank of death in Indonesia [2].

Ischemic stroke is caused by a reduction in blood flow to the brain. Based on the AHA consensus 2013, ischemic stroke is defined as an episode of neurological dysfunction caused by cerebral infarction [3]. The disease accounts for 87% of all acute stroke occurrences. Hence, in the past decade, various studies have been done to improve the understanding of the pathophysiology, diagnosis, and therapy of ischemic stroke [4].

Brain washing procedure carried out in Indonesia since 2012 up to now, is intended as an alternative therapy for treating both acute and chronic ischemic stroke. The method used in brainwashing is DSA with IAHF. This procedure is welcomed especially by stroke patients who experienced residual symptoms and gave burdens to their families. They consider this is a new way to treat the disabilities of stroke patients.

Intra Arterial Heparin Flushing in Cerebral DSA

The journey of angiography of the brain was started in 1927 by Egaz Moniz, a neurologist from Portugal. This procedure was called as a Cerebral Arteriography. He performed an injection of contrast through an internal carotid artery and pictured the contrast that filled the blood vessel. At the same year, he published his worked in *Review Neurologie* journal. Further development, noted the efforts of neurointervention to find the right kind of contrast to produce an optimize picture. The DSA introduced in 1979 by Charles Mistretta, was a method To view the arterial system through the injection of intra-arterial contrast that is captured by the x-ray. Because the feature of the bones had been suppressed, by this method, the clinicians were more attention to focus on the imagery of the blood vessels (Usman et al., 2014).

Diagnostic angiography procedures have been done at an early stage neurointervention. This cerebral DSA becomes a gold standard as a diagnostic procedure in viewing the picture of the cerebral vessels, especially for detect brain/spinal aneurysm or vascular

***Corresponding author:** Moh Hasan Machfoed, Department of Neurology, Medical Faculty of Airlangga University, Dr Soetomo Hospital, Surabaya, Indonesia, E-mail: mh.machfoed@gmail.com

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malformation (Usman et al., 2012). The use of DSA has several advantages in terms of the following: (1) physical description; (2) detection, accuracy and sensitivity; (3) diagnostic decision makes [5].

In every procedure of cerebral DSA, heparin is used to reduce the formation of thrombotic coating on the outer surface of the catheter, clot formation in the catheter, and prevents thromboembolic complications [6]. A bolus of 40-60 IU/kg of heparin was administered at the beginning of the procedure, and heparinized saline solution was used for intermittent flushing of the catheter (Usman et al, 2012).

In the past ten years, a number of studies about the risk of cerebral DSA, have shown that the proportion of neurological complications that occur during the procedure has been 0.05%-2.9%. While the proportion of non-neurological complications has been 0.05%-14.7%. The mortality risk has been around 0.05%-0.08% (Usman et al 2012).

IAAF is a modification of angiography using DSA. Heparin flushing is done with a catheter guide. The use of heparin either as a bolus or diluted with saline as the fluid flushing of catheters, has long been known in the procedures of interventional radiology [6].

The occurrence of thrombus formation at the entry site of the catheter is around 0.4-2.3% The complication that comes in a thromboembolic formation at angiography does not occur at the site of entry only, but also at the catheter and the guide wire being used [7]. Catheter with a specific material such as polyurethane is less thrombogenic than that of other materials (polyethylene, vinyl chloride, selastic). Regardless the material used, the catheter must be soaked with heparin flushing before the angiography [8].

The usage of systemic heparinization can be effective with combination of intra-arterial direct injection through the catheter in the beginning of the procedure (3000 U bolus) with intermittent flushing, using a dilute solution of heparinized saline (5000 U/500 cc saline) [9].

Nowadays, the usage of heparin at the transfemoral cerebral angiography is given in a variety of dose. Heparin can be given through either trans-arterial sheath in a continuous flushing (4000 U/L) or through combination of intravenous heparin (100U/kg) or at maximum dose of 2000U [10]. A larger dose of more than 6000U/L is given as continuous flushing at the sheath and intermittent flushing during procedure [11].

Heparin used in interventional procedures like DSA, aims to reduce the formation of thrombotic coating on the outer surface of the catheter, clot formation in the catheter, and prevents thromboembolic complications [6].

Biological Mechanisms of Heparin

Heparin is extraordinary because of its variability. Since it was first introduced in 1916 [12], a long-lasting debate has ran regarding its structure and anticoagulant properties [13, 14]. Chemically, it is a collection of fragments, each with different molecular weights and different modes of action. The most important action of heparin is its interference in the coagulation cascade [14].

Generally, heparin acts on different levels of the coagulation cascade. Its properties can be defined as anti-inflammatory [15, 16] anticoagulative, antithrombotic, pro-fibrinolytic, anti-aggregative, anti-proliferative and anti-ischemic [17, 18]. Recently, a clear change in the main use of heparin, as well as low-molecular weight heparins has been advocated representing a shift from treatment and prophylaxis of deep vein thrombosis to prophylaxis of thromboembolic disease following vascular, cardiovascular or orthopedic surgery, treatment of unstable angina and prevention of acute myocardial infarction [18].

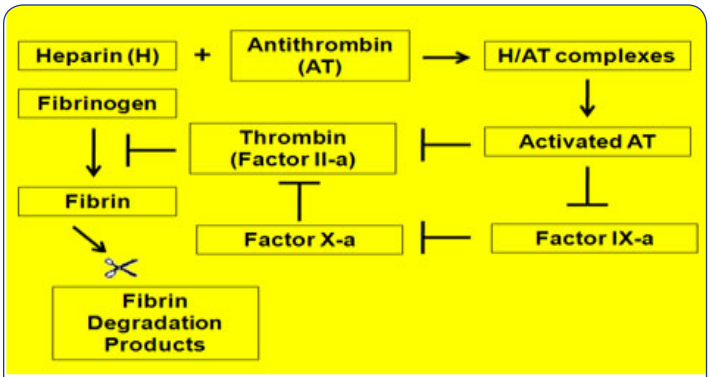

Fig 1: Biological Mechanisms of Heparin

The anticoagulation effect of heparin occurs with the help of a plasmatic cofactor that is antithrombin (AT). Heparin binds to AT and forms a stable covalent heparin-AT complexes (H/AT complexes). The H/AT complexes will activate (the symbol of →) AT becomes activated AT. Then, the activated AT will inactivate (the symbol of –I) thrombin (factor IIa), activated factor IX (IXa) and activated factor X (Xa). Finally, inactivated thrombin will inhibit the change of fibrinogen into fibrin that ultimately led to the fibrin degradation products.

The anticoagulation effect of heparin occurs with the help of a plasmatic cofactor. Heparin itself does not have any anticoagulation properties. The cofactor is antithrombin (AT). Heparin binds to antithrombin through the unique pentasaccharide sequence present in its molecule, and forms stable covalent AT-heparin complexes (AT/H complexes). Then, the complexes inactivate both thrombin (factor IIa) and activated factor X (Xa) at approximately the same level. Similarly, activated factor IX (IXa) is inhibited by the AT/H complex. To trigger inhibition of thrombin by the AT/H complex, not only the pentasaccharide terminal is required, but additionally the heparin molecule ought to be big enough to create a bridge between thrombin and antithrombin [19].

As mentioned, antithrombin is a major cofactor of heparin; however it is not the only one. A high concentration of heparin potentiates thrombin inhibition in an antithrombin-independent manner, through another cofactor, known as heparin cofactor II (HCII). This catalysis is also molecular weight-dependent, as it requires heparin to carry at least 24 saccharide units [20]. *In vivo,* heparin binds to platelets and then, depending on the conditions, can accelerate or inhibit platelet aggregation. Generally, high molecular weight heparin with low affinity to factor Xa affects

the platelets more than low molecular weight heparins with high affinity to factor Xa.

Heparin increases coagulation times in humans [21]. Moreover, it increases the vessel wall permeability. The interaction of heparin with platelets and vascular endothelial cells can contribute to heparin-induced bleeding in a manner, independent of its previously described anticoagulant properties. Generally, heparin disturbs homeostasis through inhibition of coagulation enzymes. This effect is facilitated by plasma cofactors and through inhibition of platelets [18].

Heparin is thought to enhance thrombolytic by inhibiting TAFI (thrombin activatable fibrinolysis inhibitor), a carboxypeptidase that inhibits fibrinolysis. A study of Colucci showed that heparin is unable to stimulate fibrinolysis through a TAFI-dependent mechanism, most likely because of its inefficiency in inhibiting thrombin generation on the clot surface [22].

The Use of Heparin in Clinical Practices

The main effect of heparin lies in its anticoagulant activity. Heparin is involved in different pathways of the coagulation cascade with anticoagulant, antithrombotic, profibrinolytic, anti-aggregative, as well as anti-inflammatory effects. Moreover, there is a little doubt about their anti-proliferative and anti-ischemic activity [23].

The American College of Chest Physicians (ACCP), recommended the use of heparin in the following indications:

1. Prophylaxis of deep vein thrombosis in general surgery, gynecology and urology, in middle-and high-risk patients, in total hip replacement and hip arthroplasty, as well as in neurosurgery.
2. Prophylaxis of VTE in acute myocardial infarction or acute stroke, and in high-risk patients with multiple disorders
3. Treatment of deep vein thrombosis.
4. Early treatment of an acute myocardial infarction (AMI) using thrombolytic or in patients at risk of embolization; in AMI treatment, a combination of heparin with acetyl salicylic acid (ASA) is recommended.
5. Early treatment of an unstable angina pectoris; Uncomplicated percutaneous coronary angioplasty (PCA).
6. Treatment of cardio embolic disease affecting large vessels, especially in connection with risk of VTE.
7. Peripheral vascular reconstructive surgery.
8. Cardio version in patients suffering from atrial fibrillation, during cardiopulmonary bypass, during intra-arterial balloon contra-pulsation and hemodialysis.
9. Treatment of cerebral sinus venosus thrombosis.
10. Treatment of aseptic thrombotic endocarditis and embolization.
11. Prophylaxis of patients with disseminated carcinoma and aseptic valvular proliferation.
12. Selected cases of disseminated intravascular coagulopathy.
13. Prophylaxis of pediatric patients following Blalock-Taussig shunt or following Fontan procedure.
14. Prophylaxis in pregnant and post-parturition women with a history of deep vein thrombosis - replacement of coumarin derivatives, at least till 13 week of gravidity and again in the 3rd trimester
15. Recommended especially in thrombophilic women with repeated abortions, preeclampsia, placental disorders and/or intrauterine growth deformity of the fetus.
16. Anticoagulation of blood collected for laboratory analysis and of catheters and cannulas during regular patient care of several clinical conditions mentioned above, there is no statement mentioning that heparin can be used as treatment of acute and chronic ischemic stroke [24].

Pathophysiological Cascades of Ischemic Stroke

Ischemic stroke may manifest in the form of thrombotic stroke (large vessel and small vessel types); embolic stroke (with/without known cardiac and/or arterial factor); systemic hypo perfusion (Watershed or Border Zone stroke); or venous thrombosis [25].

Irrespective of the cause, compromised vascular supply to the brain is the primary event in majority (85–90%) of acute stroke. Low respiratory reserve and complete dependence on aerobic metabolism make brain tissue particularly vulnerable to effects of ischemia. A spectrum of severity is generally observed in the affected region of the brain, owing to the presence of collateral circulation. Thus, part of the brain parenchyma (core) undergoes immediate death, while others may only be partially injured with potential to recover (penumbra) [25].

Cerebrovascular tissue undergoing ischemia has two layers: (1) inner core of severe ischemia with blood flow below 10–25%, displaying necrosis of both neuronal as well as supporting glial elements; and (2) outer layer of less severe ischemia (penumbra), supplied by collaterals, and contain cells which can be retrieved by timely therapeutic intervention.

Following an ischemic event, the centre of the core is perfused at 10–12 ml/100 g/min or less, while the ischemic area around it (surrounded by the penumbra) is critically hypoperfused at less than 18–20 ml/100 g/min and is at risk of dying within hours. In contrast, the penumbra is perfused at less likely at approximately 60 ml/100 g/min and is less likely to die [26]. The optimal reported CBF thresholds varied widely, from 14.1 to 35.0 and from 4.8 to 8.4 mL/100 g per minute for penumbra and infarct core, respectively. Neurons in the penumbra are mostly dysfunctional, but may recover if reperfused in time [27].

In the area of reduced blood supply, adenosine triphosphate (ATP) consumption continues despite insufficient synthesis, causing total ATP levels to drop and lactate acidosis to develop with concomitant loss of ionic homeostasis in neurons. Once this initial step has taken place, an ischemic cascade follows involving a multimodal and multicell series of downstream mechanisms [28].

Ischemic stroke can occur due to the obstruction of clot. In the area

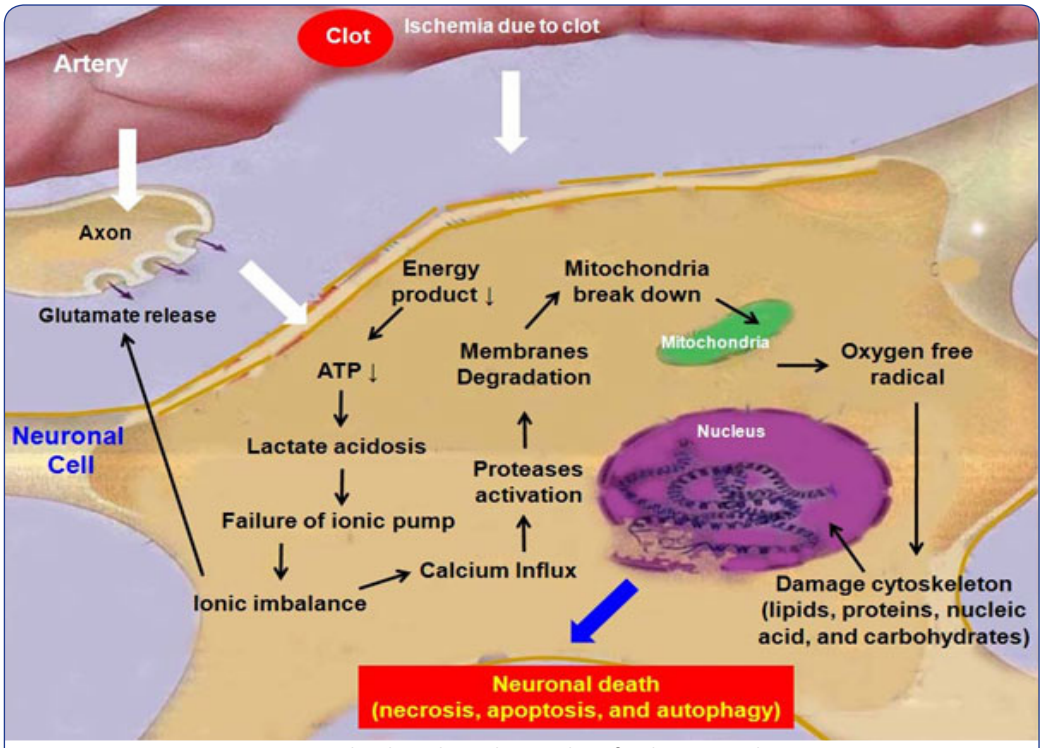

Fig 2: Pathophysiological Cascades of Ischemic Stroke

of reduced blood supply, there is a decline in energy production that causes the decrease of ATP level, and followed by lactate acidosis and ionic homeostasis disruption. Lactate acidosis causes ion pump failure and ionic imbalance.

The imbalance of ion causes calcium influx into neuronal cells. The high level of calcium ions within the cells led to the activation of proteases, degradation of membranes and cause damage to the mitochondria. Damage to mitochondria causes an increased production of oxygen free radicals that can damage the nucleus and cytoskeleton. Ultimately, these multimodal cascades will result in a complex mix of neuronal death comprising of necrosis, apoptosis, and autophagy.

Severe cerebral ischemia leads to a loss of e energy stores resulting in ionic imbalance and neurotransmitter release and inhibition of reuptake. It is especially the case for glutamate, the main excitotoxic neurotransmitter. Glutamate binds to ion tropic N-Methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors promoting a major influx of calcium. This calcium overload triggers phospholipases and proteases that degrade essential membranes and proteins. The broken cell's membrane, it becomes more permeable, and more ions and harmful chemicals flow into the cell. Mitochondria break down, releasing toxins and apoptotic factors into the cell. The caspase-dependent apoptosis cascade is initiated, causing cells to "commit suicide." In addition, the glutamate receptors promote an excessive sodium and water influx with concomitant cell swelling, edema and shrinking of extracellular space. Massive calcium influx activates a catabolic process mediated by proteases, lipases, and nucleases [29].

High calcium, sodium, and adenosine diphosphate (ADP) levels in ischemic cells stimulate excessive mitochondrial oxygen radical production within other sources of free radicals production such as prostaglandin synthesis and degradation of hypoxanthine. These reactive oxygen species (ROS) directly damage lipids, proteins, nucleic acid, and carbohydrates [30].

Downstream of free radicals, other neuronal death mechanisms will also be induced involving, e.g. mitochondrial transition pore formation [31], the lipoxygenase cascade [32], the activation of poly ADP-ribose polymerase (PARP) [33] and amplified ionic imbalance via secondary recruitment of calcium-permeable transient receptor potential ion (TRPM) channels [34]. Furthermore, ROS and reactive nitrogen species also has the potential of modifying endogenous functions of proteins, which may be neuroprotective [35]. Ultimately, these multimodal cascades will result in a complex mix of neuronal death comprising necrosis, apoptosis, and autophagy [36], Fig 2.

The post-stroke angiogenesis is the key step for recovery after ischemia and provide the critical neurovascular substrates for neuronal remodeling after stroke. In the process of angiogenesis, loss of vascular integrity and degradation of cell matrix are crucial initiating steps. Matrix metalloproteinase (MMPs) degrade the extracellular matrix and prepare the stage for growth factors and guidance molecules [37].

This forms the basis of current protocols which favor early pharmacologic intervention for re-canalization of occluded vessel. It will not only salvage neuronal and glial cells from penumbra, but also glial cells from the central ischemic core zone, thereby markedly limiting the size of infracted tissue [38].

CBF in Ischemic Stroke

CBF is the blood supply to the brain tissue, which plays a role in providing oxygen and nutrients. When the blood supply is interrupted, there will be a disruption of brain function that would cause morbidity and mortality (Detre et al., 2012).

Under normal conditions, the CBF is regulated by auto regulation mechanism of the brain. The CBF is maintained in the range of 60 to 100mL/100g/ min, with a central perfusion pressure (CPP) in the range of 60 to 160 mmHg. Auto regulation ability will disappear when blood pressure is less/more than 60 to 160 mmHg. In this condition, CBF became dependent on mean arterial pressure (MAP) [39].

A decrease in CBF will be compensated by an increase in oxygen extraction. When CBF drops below a certain value, the ability to increase oxygen extraction will be lost. This leads to functional, biochemical, and structural changes, which ultimately results in irreversible neuronal cell death [27]. The brain has a high demand for oxygen and glucose to energy production. This high metabolic demand causes the brain to be vulnerable to the decline of CBF [40].

CBF disruption either focal or global, results in limited fulfillment of the substrate, causing changes in brain activity that led to the failure of energy production [41]. Animal studies indicated that some time after ischemia, the concentration of glucose, glycogen, adenosine triphosphate (ATP) and phosphocreatinine (PCr) decrease rapidly, and almost completely disappear within 10-12 minutes of ischemia [40].

Protein synthesis is inhibited at CBF less than 50ml/100g/min and obstacles complete at the level of CBF below 35ml/100g/min. The use of sugar and energy metabolism increases at this level, but it experiences a sharp decline if CBF level below 25ml/100g/min. In this circumstance occurs an anaerobic glycolysis and edema [40].

Damage due to induced sodium ions, causes an increase in cytosolic calcium, ATP depletion, and the release of glutamate. Glutamate is a neurotransmitter that activates destroyed enzymes like lipase, protease, and nuclease causing neuronal tissue breakdown. Free radical formation also increases in the initial period after ischemia [40].

A decrease in CBF below 16-18 ml/100g/min results in a decrease of the electrical activity of either spontaneous or spark. At this level, the function of electrical neuronal lost (electrical failure) [42]. When CBF decreases into 10-12ml/100g/min, an anoxic depolarization will happen. This depolarization will be followed by ion hemostasis disorders, changes in intra and extracellular electrolyte composition, decreased ATP and malfunction of membrane (membrane failure). The failure of membrane function causes the decreased of extracellular sodium, chloride and calcium as well as a decrease of potassium efflux to the extracellular and resulting in an increase in intracellular calcium by up to 25% [40, 42].

Ischemic stroke is caused by a reduction in blood flow to the brain. Hence, the decrease in CBF has received an effective answer: accelerated reperfusion via thrombolytic using rt-PA is associated with an improved clinical outcome. This achievement is now routinely transferred to practice. This ease of translation is due to the fact that the underlying conceptual model is simple: an arterial occlusion decreases CBF. So an effective treatment should increase CBF [43].

Restoring CBF is an obvious and primary goal. But ischemia–reperfusion itself can also set off numerous cascades of secondary injury. Reactive radicals will be generated, blood–brain barrier integrity may be compromised, and multimodal neuronal death processes composed of programmed necrosis, apoptosis, and autophagy may still continue unabated [43].

Treatment of Acute Ischemic Stroke

In 2013, the American Heart Association (AHA)/American Stroke Association (ASA) published a Guideline for the Early Management of Patients with Acute Ischemic Stroke. The purpose of the paper was to present an overview of the current evidence and management recommendations for evaluation and treatment of adults with acute ischemic stroke, within the first 48 hours from stroke onset. The goal of these guidelines is to limit the morbidity and mortality associated with stroke. The guideline discusses early stroke evaluation and general medical care, as well as ischemic stroke, specific interventions such as reperfusion strategies, and general physiological optimization for cerebral resuscitation [44].

Intravenous administration of rtPA (IV rtPA) remains the only FDA approved pharmacological therapy for treatment of patients with acute ischemic stroke [45]. Its use is associated with improved outcomes for a broad spectrum of patients who can be treated within 3 hours of the last known well time before symptom onset and a mildly more selective spectrum of patients who can be treated between 3 and 4.5 hours of the last known well time. Most importantly, earlier treatment is more likely to result in a favorable outcome. Patients within 3 hours of onset with major strokes (NIHSS score >22) have a very poor prognosis, but some positive treatment effect with IV rtPA remains. Treatment with intravenous rtPA is associated with increased rates of intracranial hemorrhage, which may be fatal [46].

A number of techniques and devices are under study in several trials. Although several devices have resulted in recanalization with acceptable safety, direct comparative data between the devices are not available. The combination of pharmacological fibrinolysis and mechanical thrombectomy appears to have the highest rate of recanalization without any difference in rate of intracranial hemorrhage. Consistently, recanalization rates in trials exceed rates of the best clinical outcomes, which suggest the importance of patient selection independent of the technical effectiveness of thrombectomy devices. As with the intra-arterial administration of fibrinolytics, the use of these devices will be limited to those CSCs that have the resources and physician expertise to perform these procedures safely [46]. Lastly, as with intravenous fibrinolysis, *time is brain* for all forms of endovascular reperfusion, and all efforts must be made to reduce time to reperfusion, because the likelihood of favorable outcome is directly linked to the time to reperfusion [47].

The International Stroke Trial (IST) tested subcutaneously administered unfractionated heparin (UFH) in doses of 5000 or 25 000 U/d started within 48 hours of stroke (International

Stroke Trial Collaborative Group, 1997). Dual randomization meant that approximately half of the patients receiving heparin were also prescribed aspirin. Neither monitoring of the level of anticoagulation nor adjustment of dosages in response to levels of anticoagulation was performed. In addition, some patients did not have a brain imaging study before entry into the trial, and thus, some patients with hemorrhagic stroke may have been enrolled. Although heparin was effective in lowering the risk of early recurrent stroke, an increased rate of bleeding complications negated this benefit. A subgroup analysis did not find a benefit from heparin in lowering the risk of recurrent stroke among those patients with atrial fibrillation [48]. Other studies of anticoagulation similarly failed to show definitive benefit. A Swedish study failed to demonstrate a benefit from heparin for treatment of patients with progressing stroke [49].

Eriksson examined "Discarding Heparins as Treatment for Progressive Stroke in Sweden 2001 to 2008". The conclusion of the study stated that there is no immediate, stepwise effect of new scientific information and national guidelines on clinical practice concerning heparin as treatment for progressive ischemic stroke [50].

Chung studied trends in the intravenous heparin use during a 6-year time period and the potential influence of clinical guidelines in national language on intravenous heparin for the treatment of acute ischemic stroke administration in Korea. The conclusions showed that the use of intravenous heparin for acute ischemic stroke treatment has decreased in Korea, and this change may be attributable to the spread and successful implementation of regional clinical practice guidelines [51].

Treatment of Chronic Ischemic Stroke

Up to now, have been no studies or guidelines that are universally agree concerning the treatment of chronic ischemic stroke. Several fragmented studies mentioned that a particular method can improve the clinical condition of patients with chronic ischemic stroke [52]. Among them are the uses of medical rehabilitation, stem cells and others.

Approximately one third of heparin's molecular weight is represented by a unique pentasaccharide that is necessary for binding to antithrombin, accelerating thrombin and activated factor X inhibition [53]. An additional anticoagulant activity of heparin goes through heparin cofactor II activation, which is less potent and generally requires higher systemic concentrations of heparin. The remainder of the heparin molecule does not possess any anticoagulant properties.

Stroke treatments need to promote neuroplasticity to improve motor function. Physical exercise is considered as a major candidate for ultimately promoting neural plasticity and could be used for different purposes in human. First, acute exercise could be used as a diagnostic tool to understand new neural mechanisms underlying stroke physiopathology. Secondly, it is well established that physical exercise training is advised as an effective rehabilitation tool. Indeed, it reduces inflammatory processes and apoptotic marker expression, promotes brain angiogenesis and expression of some growth factors, and improves the activation of affected muscles during exercise. Nevertheless, exercise training might also aggravate sensor motor deficits and brain injury depending on the chosen exercise parameters. For the last few years, physical training has been combined with pharmacological treatments to accentuate and/or accelerate beneficial neural and motor effects. Finally, physical exercise might also be considered as a major nonpharmacological preventive strategy that provides neuroprotective effects reducing adverse effects of brain ischemia [52].

Previous data suggest that the amount and aerobic intensity of stepping training may improve walking post stroke. Recent animal and human studies suggest that training in challenging and variable contexts can also improve locomotors function. Such practice may elicit substantial stepping errors, although alterations in locomotors strategies to correct these errors could lead to improved walking ability. The study of Holleran et al suggests that stepping training at high aerobic intensities in variable contexts was tolerated by participants post stroke, with significant locomotors improvements [54].

The regenerative potential of brain has led to emerging therapies that can cure clinico-motor deficits after neurological diseases. Bone marrow mononuclear cell therapy is a great hope to mankind as these cells are feasible, multipotent and aid in neurofunctional gains in stroke patients. Bhasin evaluated safety, feasibility and efficacy of autologous mononuclear (MNC) stem cell transplantation in patients with chronic ischemic stroke (CIS) using clinical scores and functional imaging (fMRI and DTI). The result showed that there was an increased number of cluster activation of Brodmann areas BA 4, BA 6 post stem cell infusion compared to controls indicating neural plasticity. Cell therapy is safe and feasible which may facilitate restoration of function in CIS [55].

Cell therapy is emerging as a viable therapy to restore neurological function after stroke. Many types of stem/progenitor cells from different sources have been explored for their feasibility and efficacy for the treatment of stroke. Transplanted cells not only have the potential to replace the lost circuitry, but also produce growth and tropic factors, or stimulate the release of such factors from host brain cells, thereby enhancing endogenous brain repair processes. Although stem/progenitor cells have shown a promising role in ischemic stroke in experimental studies as well as initial clinical pilot studies, cellular therapy is still at an early stage in humans. Many critical issues need to be addressed including the therapeutic time window, cell type selection, delivery route, and *in vivo* monitoring of their migration pattern. Liau concluded that cell therapies can be used as a neurorestorative regimen in the management of chronic ischemic stroke [56].

Anticoagulants Treatment in Ischemic Stroke

Here are the recommendations of the AHA/ASA Guidelines for the Early Management of Patients with Acute Ischemic Stroke:

1. At present, the usefulness of argatroban or other thrombin inhibitors for treatment of patients with acute ischemic stroke is not well established.
2. The usefulness of urgent anticoagulation in patients with severe

stenosis of an internal carotid artery ipsilateral to an ischemic stroke is not well established.

3. Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke, is not recommended for treatment of patients with acute ischemic stroke.

4. Urgent anticoagulation for the management of noncerebrovascular conditions is not recommended for patients with moderate-to-severe strokes because of an increased risk of serious intracranial hemorrhagic complications.

5. Initiation of anticoagulant therapy within 24 hours of treatment with intravenous rtPA is not recommended [44].

Summary

Intra Arterial Heparin Flushing in Cerebral DSA

In every procedure of cerebral DSA, heparin is used to reduce the formation of thrombotic coating, and prevents thromboembolic complications. Without being followed by other procedures, such as stenting or coiling, then the act of cerebral DSA is only a diagnostic not therapeutic procedure. No references mentioning that the cerebral angiography with heparin can be used for the management of ischemic stroke either acute or chronic [6, 7, 8, 9, 11, 57].

Biological Mechanisms of Heparin

There is a change in the main use of heparin, from treatment and prophylaxis of deep vein thrombosis to prophylaxis of thromboembolic disease following vascular, cardiovascular or orthopedic surgery, treatment of unstable angina and prevention of acute myocardial infarction. Heparin was not able to destroy the clot that occurs in acute and chronic ischemic stroke [18].

Treatment of Ischemic Stroke

The AHA/ASA guidelines (2013), recommended that rtPA can be used in the treatment of acute ischemic stroke. Heparin was not beneficial in lowering the risk of recurrent stroke among those patients with atrial fibrillation. Heparin failed for treatment of patients with progressing stroke. There was no immediate, stepwise effect of new scientific information and national guidelines on clinical practice concerning heparin as treatment for progressive ischemic stroke. The use of heparin for acute ischemic stroke treatment has decreased in Korea, and this change may be attributable to the successful implementation of regional clinical practice guidelines [44, 48, 49, 50, 51]. There were no studies supporting that heparin was useful for the treatment of acute and chronic ischemic stroke [52, 54, 55, 56].

Conclusion

From all discussion above, it is concluded that IAHF in brain washing procedure is not in accordance with the applied scientific principles and does not have any literatures and guidelines that support the benefits of heparin in acute and chronic ischemic stroke.

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