

Review article:

DOES INTRA-ARTERIAL HEPARIN FLUSHING (IAHF) CAN ACTUALLY INCREASE MANUAL MUSCLE TEST (MMT) SCORE IN CHRONIC ISCHEMIC STROKE PATIENTS?

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ABSTRAK

Stroke masih merupakan masalah kesehatan utama di dunia. Stroke iskemik menyumbang 87% dari semua kemunculan stroke akut. Pada tahun 2013, American Heart Association (AHA)/Amerika Stroke Association (ASA), menerbitkan Pedoman Pengelolaan Awal Pasien Stroke Iskemik Akut. Managemennya terdiri dari penggunaan rekombinan jaringan aktivator plasminogen (rtPA), pengobatan endovascular, dll. Tidak seperti stroke iskemik akut, sampai sekarang, tidak ada pedoman yang disediakan mengenai manajemen stroke iskemik akut yang disetujui secara universal. Hasil penelitian dengan judul "Intra Arteri Heparin Flushing Meningkatkan Pedoman Uji Muscle - Medical Research Council (MMT-MRC) Score di kronis Stroke Pasien Iskemik" sangat menarik, karena merupakan upaya baru untuk mengobati pasien dengan stroke iskemik akut. Tujuan artikel ini adalah untuk meninjau studi yang disebutkan di atas, sesuai dengan prinsip-prinsip ilmiah berdasarkan pedoman dan literatur standar. Review kami terbatas hanya untuk pembahasan hasil penelitian. Dari diskusi ini dapat dibuktikan bahwa referensi yang ada yang mendukung dan atau menolak hasil studi. Berdasarkan diskusi dan simpulan dari penelitian ini, tidak ada referensi yang mendukung bahwa IAHF dapat meningkatkan fungsi motorik (otot) pasien dengan stroke iskemik akut. (FMI 2016;52:148-153)

Kata kunci: *stroke iskemik akut, intra-arterial heparin flusing (IAHF), manual muscle test (MMT), fungsi motorik*

ABSTRACT

Stroke is still a major health problem in the world. Ischemic stroke accounts for 87% of all acute stroke occurrences. 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, etc. Unlike acute ischemic stroke, until now, no guidelines have been provided about the management of chronic ischemic stroke that approved universally. The result of the study with the title of "Intra Arterial Heparin Flushing Increases Manual Muscle Test – Medical Research Councils (MMT-MRC) Score in Chronic Ischemic Stroke Patient" is very interesting, because it is a new attempt to treat patients with chronic ischemic stroke. The purpose of this article is to review the study mentioned above, in accordance with the applied scientific principles and is based on the standard literatures and guidelines. Our review is limited only to the discussion of the study results. From this discussion can be proved the existing references that support and/or refuse the study results. Based on the discussions and conclusions of this study, there were no references to support that IAHF can improve motor functions (muscles) in patients with chronic ischemic stroke. (FMI 2016;52:148-153)

Keywords: *chronic ischemic stroke, intra-arterial heparin flusing (IAHF), manual muscle test (MMT), motor function*

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INTRODUCTION

Stroke is a major cause of mortality and disability worldwide (Mathers & Loncar 2006). According to the data of Ministry of Health, stroke is the first rank of death in Indonesia (Ministry of Health 2013). 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 (Sacco et al 2013). 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 (Coull et al 2002).

The objective of the study by Putranto was to find possible improvement of Manual Muscle Test (MMT) Score after administration of Intra Arterial Heparin Flushing in chronic ischemic stroke patient. The results found higher score of MMTMRC scoring system on chronic stroke patient with IAHF procedure (mean

MMT-MRC Score = 6.05 point. With $p < 0.05$). Indicating that IAHF procedure is associated with better muscle strength improvement shown with higher MMT-MRC score on stroke patient, which will have better prognostic outcome in their recovery. The conclusions of study showed that Intra Arterial Heparin Flushing have significant effect on chronic stroke patient with decreased muscle strength, which shows a significant increase of MMTMRC score (Putranto et al 2016).

INTRA ARTERIAL HEPARIN FLUSHING IN CEREBRAL DSA

The cerebral DSA becomes a gold standard as a diagnostic procedure in viewing the picture of the cerebral vessels (Usman 2012). 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 (Durran & Watts 2012).

BIOLOGICAL MECHANISMS OF HEPARIN

Generally, heparin acts on different levels of the coagulation cascade. Its properties can be defined as anti-inflammatory (Perretti & Page 2000, Salas et al 2000), anticoagulative, antithrombotic, pro-fibrinolytic, anti-aggregative, anti-proliferative and anti-ischemic (Lundin et al 2000, Dvorak et al 2010). 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 (Dvorak et al 2010).

Heparin increases coagulation times in humans (Ockelford et al 1982). Moreover, it increases the vessel wall permeability. Generally, heparin disturbs homeostasis through inhibition of coagulation enzymes. This effect is facilitated by plasma cofactors and through inhibition of platelets (Dvorak et al 2010). 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 (Colucci et al 2002).

THE USE OF HEPARIN IN CLINICAL PRACTICES

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; (2) Prophylaxis of VTE in acute myocardial infarction or acute stroke; (3) Treatment of deep vein thrombosis; (4) coronary diseases; (5) etc (Mueller 2004).

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 (Jauch et al 2013). Intravenous administration of rtPA (IV rtPA) remains the only FDA approved pharmacological therapy for treatment of patients with acute ischemic stroke (Adam et al 2005) 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 (Qureshi et al 2005).

The combination of pharmacological fibrinolysis and mechanical thrombectomy appears to have the highest rate of recanalization without any difference in rate of intracranial hemorrhage (Qureshi et al 2008). 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). 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 (Saxena et al 2001).

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 (Röden-Jüllig & Britton 2000). There was no immediate, stepwise effect of new scientific information and national guidelines on clinical practice concerning heparin as treatment for progressive ischemic stroke (Eriksson et al 2010). 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 (Chung et al 2016).

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 (Pin-Barre & Laurin 2015). Among them are the uses of medical rehabilitation, stem cells and others. 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 (Pin-Barre & Laurin 2015). Previous data suggest that the amount and aerobic intensity of stepping training may improve walking post stroke (Holleran et al 2014).

The result of a studi 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 (Bhasin et al 2012). 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 (Liu et al 2014).

ANTICOAGULANTS TREATMENT IN ISCHEMIC STROKE

Here are the recommendations of the AHA/ASA Guidelines for the Early Management of Patients With Acute Ischemic Stroke: At present, the usefulness of argatroban or other thrombin inhibitors for treatment of patients with acute ischemic stroke is not well established. The usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke is not well established.

Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsen-ing, or improving outcomes after acute ischemic stroke, is not recommended for treatment of patients with acute ischemic stroke. 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. Initiation of anticoagulant therapy within 24 hours of treatment with intravenous rtPA is not recom-mended (Jauch et al 2013).

REVIEWS OF THE STUDY

In the discussion: had been discussed at length about the Anatomy of Movement as follows “The motoric function of our body is managed by motor cortex in our brain. In stroke patients with paresis, the neuron output impulse was decreased because of the decrease of motor neuronsetc”. (Schwerin 2013). This is the abstract of Schwerin (2013): Almost all of behavior involves motor function, from talking to gesturing to walking. But even a simple movement like reaching out to pick up a glass of water can be a complex motor task to study. Not only does your brain have to figure out which muscles to contract and in which order to steer your hand to the glass, it also has to estimate the force needed to pick up the glass. Other factors, like how much water is in the glass and what material the glass is made from, also influence the brains calculations. Not surprisingly, there are many anatomical regions which are involved in motor function. The primary motor cortex (M1) lies along the precentral gyrus, and generates the signals that control the execution of movement. Secondary motor areas are involved in motor planning. The reference of Schwerin did not mention that the impaired motor function in the cerebral cortex as a result of stroke can be treated with IAHF.

In the discussion was written as follows: “Lesion in motor cortex especially in M1 region in stroke accident and brain trauma will ended up as necrosis in focal area that finally will cause the loss of M1 output to spinal cord and in the end will cause functional disability” (Guggenmos et al 2013). This is the abstract of Guggenmos: “Neural interface systems are becoming increasingly more feasible for brain repair strategies. This paper tests the hypothesis that recovery after brain injury can be facilitated by a neural prosthesis serving as a communication link between distant locations in the cerebral cortex. The primary motor area in the cerebral cortex was injured in a rat model of focal brain injury, disrupting communication between motor and somatosensory areas and resulting in impaired reaching and grasping abilities. After implantation of microelectrodes in cerebral cortex, a neural prosthesis discriminated action potentials (spikes) in premotor cortex that triggered electrical stimulation in somatosensory cortex continuously over subsequent weeks. Within 1 wk, while receiving spike-triggered stimulation, rats showed substantially improved reaching and grasping functions that were indistinguishable from prelesion levels by 2 wk. Post hoc analysis of the spikes evoked by the stimulation provides compelling evidence that the

neural prosthesis enhanced functional connectivity between the two target areas. This proof of concept study demonstrates that neural interface systems can be used effectively to bridge damaged neural pathways functionally and promote recovery after brain injury” (Guggenmos et al 2013). So the reference of Guggenmos concluded that the repair of motors (muscles) caused by stroke, can occur after implantation of microelectrodes in the cerebral cortex, not because of IAHF therapy.

In the discussion was written as follows: “The normal function of muscle needs an intact connect-ion along the motor pathway (which a connection between nerves cells that elongated from brain into spinal cord and ended in muscle unit), damage in any point will decrease the brain ability to control muscle movement. The decline of this ability will cause weakness which also called paresis. MMT is a reliable diagnostic tool to measure muscle weakness on stroke patients” (Izani 2014). Aim and conclusion: the aim of study of Izani was to know the reliability of Manual Muscle Test Examination in stroke patient of RSUD Sardjito. And the conclusion was the Manual Muscle Test (MMT) has a very good reliability. Conventional testing does not require any special tools, only education and knowledge. It is easy to administer and can be used on a very large population. It gives information that is beneficial in diagnosing conditions (Izani 2014). The study of Izani about MMT was totally unrelated to the motor repair as a result of IAHF therapy in patients with chronic ischemic stroke.

In the discussion was written as follows: “Muscle weakness in chronic stroke patients might be associated with the decline of descending impulse input from motor area in brain hemisphere affected by strokeetc”. (Silva-Coto et al 2014). This is the conclusion of Silva-Coto “Low serum concentrations of IGF-1 and IGFBP-3, deficits in neuromuscular performance, selective muscle atrophy, and decreased agonist muscle activation were found in the group with chronic hemi paresis post stroke. Both hemorrhagic and ischemic stroke were considered, and the data reflect a chronic post stroke population with good function” (Silva-Coto et al 2014). So the reference of Silva-Coto concluded that muscle atrophy, voluntary activation disturbances, and low serum concentrations of IGF-1 and IGFBP-3 were associated with weakness in people with chronic stroke. And it did not conclude that the improvement of motor function was related to the IAHF treatment.

The conclusion of study wrote as follows: “Our study showed that IAHF treatment can significantly improve muscle strength, represented by MMT score in chronic

ischemic stroke patients with onset more than 30 days. So far IAHF was suggested to be a new potential stroke therapy with good prognostic outcome and wider time window”. Comment on the conclusions of study as follow: Based on the data drawn from this study and as explained above, it is concluded that no references to support that IAHF can improve motor functions (muscles) in patients with chronic ischemic stroke.

CONCLUSION

Based on the references of (1) Intra Arterial Heparin Flushing in Cerebral DSA; (2) Biological Mechanisms of Heparin; (3) The Use of Heparin in Clinical Practices; (4) Treatment of Acute Ischemic Stroke; (5) Treatment of Chronic Ischemic Stroke; (6) Anti-coagulants Treatment in Ischemic Stroke; and Comment on the conclusions of study, it is concluded that no references to support that IAHF can improve motor functions (muscles) in patients with chronic ischemic stroke.

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