Fluid Dynamic Analysis of IAHF (Intra Arterial Heparin Flushing) Stroke Therapy in Microfluidic Channel

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Abstract. Ischemic Stroke is a disease that inhibits blood supply to the brain. One method in handling ischemic stroke patient is Intra Arterial Heparin Flushing (IAHF) which has been claimed to be able to improve motoric function of a patient. However, *in vitro* clinical research to understand IAHF is scarce. One of *in vitro* methods can be applied is using microfluidic. This research aims to create a microfluidic system that can represents blood vessel system of a stroke patient and to quantify volumetric flow rate of 1,3-Propanediol (as a blood model) in microfluidic channels. Microfluidic which is made of acrylic with a *square-wave* design, is employed to represent a thrombotic ischemic stroke and embolic ischemic with the addition of wax to represent plaque in blood vessel. Various viscosity of 1,3-propanediol are applied (1.5 mPa. s; 4 mPa. s; 7.2 mPa. s) to represent the effects of heparin drug. The results indicate that fluid Reynold number in the microfluidic channel are 8.8023 $x10^{-4}$ and 12.3230 $x10^{-4}$ which is fall in the area of Reynold number laminar flow such as in blood vessels. Volumetric flow rate of 1,3-propanediol decreases when the viscosity increases and when wax is situated in the microfluidic channel. Diluted 1,3-propanediol (at a viscosity of 1.5 mpas) shows similar volumetric flow rate (when it passes through microfluidic channels with wax) with normal blood viscosity 4,0 mpas (when it passes microfluidic channels without wax). This similarity indicates an increase of blood flow when heparin is added in excess in IAHF method, which induces an improvement of organ motoric function.

1. Introduction

Stroke or cerebrovascular disease, according to the World Health Organization (WHO), are clinical signs that develop rapidly due to impaired focal or global brain function due to a blockage or rupture of blood vessels in the brain [1]. In Indonesia, based on research conducted by the Indonesian Ministry of Health in 2011, the prevalence of non-communicable diseases (PTM), especially stroke, reached 17.7% in the first place. Stroke patients who died at a young age, 45-52 years, began to cause concern since it reaches 15.9% [2].

One method of handling stroke is Intra Arterial Heparin Flushing (IAHF) which was introduced and used by doctor Terawan doctors at the Central Army Hospital (RSPAD) Gatot Soebroto, Jakarta [3]. The author argue that this method can improve motor function of patients with ischemic stroke. IAHF therapy uses a modified Digital Substraction Angiography (DSA) instrument to observe patients motoric function. After the diagnosis using DSA, followed by heparin (blood thinner) administration into the blood vessels to improve organ motoric function [4]. As a results, it is claimed that 75 patients with ischemic stroke experienced an increase of motion function limbs. However, IAHF therapy has not been clinically tested and lack of sample size. There is no complementary studies to

support the efficacy of IAHF method. Moreover, clinical trials of the effects of heparin before practicing to humans are very necessary.

Evaluation method that widely used today in drug clinical trials on living cells is by applying chemicals on cell culture in a flask. Another method that is widely used is by injecting drugs into the body of experimental animals such as mice. But this method sometimes fails to predict the reaction of drugs that will occur in the human body. Furthermore, the mentioned method is performed in a static state which does not represent the dynamic in human body. Methods using animals that, despite their DNA similarities, still show failure due to differences in metabolism and complex body structures [5].

Technological developments have led scientists to discover technologies that can overcome deficiencies that existed in previous clinical trial methods. Microfluidics is a technology that has a micron-sized channel with a channel that can represent the blood vessels and organs of living things [6]. Microfluidics can represent the shape, size, and state of the blood vessels with dynamic metabolism and circulation in the human body [6], although, to date, the complexity of the human body has not been fully represented by the presence of microfluidics. In its development, microfluidics has the potential to be applied as a platform of a pharmacological or scientific research related to medicine [5]. One example is microfluidic with trans-well (incubation) model which is an example of microvasculature blood brain barrier (BBB)model.

In this study, acrylic microfluidics with square-wave design were fabricated to represent the condition of blood vessels of ischemic stroke sufferers. Ischemic stroke represented is ischemic thrombus stroke and embolism. In ischemic thrombus stroke, blood vessels become narrowed due to the accumulation of cholesterol. This condition is represented by narrowing-widening of the channel in microfluidics in a square-wave design of 500-700 μm. Ischemic stroke embolism, which is the closure of blood vessel ducts due to accumulation of cholesterol becomes plaque, is represented by the placement of wax in the microfluidic duct.

Using this microfluidic, the flow dynamics of 1.3 propanediol representing blood are observed. Flow rate and type of flow are monitored when the viscosity of 1.3 pronanediol is varied (1.5; 4.0; 7.2 m.Pa.s). The same observation was conducted to observe flow rate and type flow when plaque is situated in the channel. Viscosity variations are used to represent the effects of heparin added to IAHF therapy since heparin dilutes blood hence reducing blood viscosity. Thus, we can obtain further information about the dynamics of the flow of 1.3 propanediol in microfluidics representing the dynamics of blood flow in the vessels in the IAHF method.

2. Experiment

2.1. Materials

Chemicals used in this experiment were waxes, aquadest and 1,3 propanediol (Merck). Microfluidic was fabricated from acrylic and the channels on microfluidic surface was carved using CNC (computer numerical control) method according to the design preferred. Square-wave design was drawn using SketchUp software (Figure 1). In this design, there are 2 channel width applied, 500 and 700 μm which is designed sequentially to represent the narrow-widening vessels due to cholesterol in thrombotic ischemic stroke.

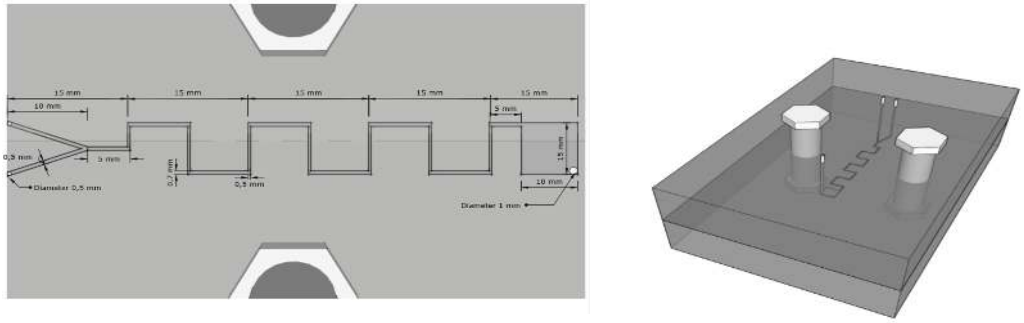

Figure 1. Schematic drawing of squarewave design using SketchUp software. Left is the schematic drawing of channels dimension while right is the 3D schematic drawing of squarewave design microfluidic

2.2. Methods

1,3 propanediol viscosity was varied to mimic blood viscosity by diluting the solution using aquadest (1,5; 4 and 7,2 mpas). The most dilute solution was used to represent blood which has been affected by heparin. Viscosity of 4 mpas mimic the normal blood viscosity while 7.2 mpas represent thick blood as effect of a disease. Wax situated in microfluidic channel was 11,21 mg to represent the clogging of blood vessel in embolic ischemic stroke. The wax was placed in 500 µm channel leaving very small entrance for the solution to pass through the vessel. Volumetric flow rate was quantified by measuring the volume of the solution coming out from the outlet at a certain duration of time.

3. Results and Discussion

3.1. Microfluidic fabricarion

Acrylic microfluidic with square-wave design has been fabricated. In this experiment setting, microfluidic is connected to a pulsatile pump which deliver 1,3 propanediol solution. The solution is kept at 35°C to mimic physiological temperature. The flow rate (rpm) of the pump was set at 72,6; 84,9 and 226,5 rpm. Pump and microfluidic is connected with tubing in inlet. To determine the quantity of solution that has passed through the channel of microfluidic, the solution coming out from the outlet is collected at a certain period of time. Thus, debit of the flow can be determined by measuring the quantity of solution collected per second. Based on this measurement the volumetric flow rate of the solution can be quantified. Figure 2 displays the fabricated microfluidic.

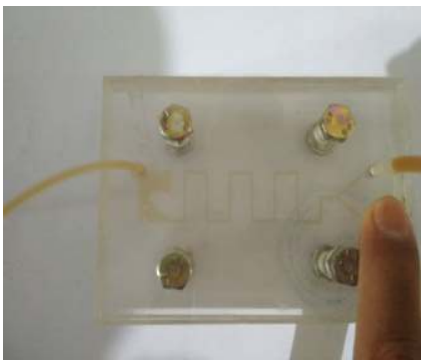

Figure 2. The fabricated microfluidic with square-wave design, inlets are situated at the left side while outlet is at the right side.

3.2. Volumetric flow rate solution in microfluidic without wax

In this system, microfluidic has narrow-widening channel width to represents thrombotic ischemic stroke. In this type of disease, blood flow experiences different pressure due to the narrow-widening blood vessels due to cholesterol accumulation in the vessel wall. Pressure changes affect flow rate of the solution which in a certain case induces stroke. Observation of flow rates representing thrombotic ischemic stroke was performed using solution of 1,3-propanediol with viscosity of 4.0 mpas, and 7.2 mpas.

1,3-propanediol with a viscosity of 4.0mpas represents blood that has been added by heparin to prevent coagulation. Viscosity of 7.2mpas represents blood without the addition of heparin. Table 1 shows data of 1,3 propanediol volumetric flow rate inside microfluidic.

Table 1. Volumetric flow rate of 1,3 propanediol

Rpm	4 mpas		7,2 mpas	
	Debit (mL/s)	Flow rate (cm/s)	Debit (mL/s)	Flow rate (cm/s)
72,6	0,1456	0,0439	0,0991	0,0299
84,9	0,2035	0,0614	0,1374	0,0414
226,5	0,2218	0,0669	0,1642	0,0495

Results show that the increasing viscosity of the solution slows down the volumetric flow rate. This indicates that inside the narrow-widening channel, solution experiences reduction of flow rate as the viscosity increases. At 4 mpas, the volumetric flow rate is 0,0439 to 0,0669 cm/s while at 7,2 mpas the flow rate decreases to 0,0299 to 0,0495 cm/s.

Viscosity is closely related with the size of the particles where higher particle size will induce more viscous solution. At viscosity of 4 mpas, it is simulated that heparin is administered into the blood and reduces the viscosity. Heparin itself is anti-coagulation agent where it prevents blood cells to coagulate and form bigger particle size. From this experiment it is evident that the dilution of the solution increases the volumetric flow rate which indicates faster blood circulation.

3.3. Volumetric flow rate solution in microfluidic with wax

To further understand fluid dynamics of solution inside a microfluidic channel which represent the blood vessel, wax was situated inside the channel to illustrate the blockage of the blood vessel by accumulation of cholesterol in embolic ischemic stroke. The solution applied in this experiment is at 4 mpas and 1,5 mpas. The latter viscosity represents the effect of excess heparin added in IAHF therapy method while 4 mpas represents normal blood viscosity. Table 2 displays volumetric flow rate of 1,5 and 4 mpas solution of 1,3 propanediol.

Table 2. Volumetric flow rate of 1,3 propanediol

Rpm	1,5 mpas		4 mpas	
	Debit (mL/s)	Flow rate (cm/s)	Debit (mL/s)	Flow rate (cm/s)
72,6	0,1269	0,0383	0,0996	0,0300
84,9	0,1870	0,0564	0,1637	0,0493
226,5	0,2065	0,0623	0,1831	0,0552

The presence of the wax in the channel reduces the flow rate of the solution at 4 mpas. In the absence of wax, the flow rate of 4 mpas solution is 0,0439 to 0,0669cm/s while in the presence of wax, the flow rate decrease to 0,0300-0,0552 cm/s. Wax inhibit the flow of the solution which then reduces the debit and flow rate. This situation increases the pressure inside the vessel which then could induce blood vessel rupture. With the addition of excess heparin which dilutes the solution, represented by 1,5 mpas solution, flow rate increases to 0,0383-0,0623. The results suggest that excess heparin restores the fluid flow rate inside the blood vessel regardless of the inhibition of flow by clogging.

3.4. Comparison of square-wave microfluidic system with arterial vascular system

Observation of the flow rate of 1.3 propanediol showed that wax was proven to inhibit the flow of fluid so that the flowrate decreased. Dilution of solution as the simulation of excess heparin addition during IAHF therapy indeed affect the flow rate observed in the channel. To analyse further the comparability of physiological conditions with quare-wave microfluidic, Reynold number was calculated to determine the type of the flow inside microfluidic channel. Mostly, the flow inside the blood vessel is categorized as laminar flow where the solution flow smoothly in a regular path. By calculating the Reynold number, it is possible to categorize the type of the flow where solution with Reynold number less than 2000 is categorized as laminar. Table 3 summarizes the comparison between two systems.

Table 3. Comparison between microfluidic system and arterial vascular system

	microfluidic	arterial vascular
Diameter (μm)	500-700	100-1000
Blood Viscosity mpas	1,5; 4,0 and 7,2	Normal at 4
Blood Flow Rate (cm/s)	0,0299-0,0699	15-19
Reynold Numbers	0,0012 and 0,00088	500
Types of flow	Laminar	laminar

Based on the comparison at Table 3, microfluidic in some aspects could satisfactorily represent physiological condition such as blood viscosity, Reynold number and flow type. However, the flow rate observed is still below the actual number which opens the opportunity for further improvement of the model.

,3 propanediol viscosity was varied to mimic blood viscosity by diluting the solution using aquadest (1,5; 4 and 7,2 mpas). The most dilute solution was used to represent blood which has been affected by heparin. Viscosity of 4 mpas mimic the normal blood viscosity while 7.2 mpas represent thick blood as effect of a disease. Wax situated in microfluidic channel was 11,21 mg to represent the clogging of blood vessel in embolic ischemic stroke. The wax was placed in 500 μm channel leaving very small entrance for the solution to pass through the vessel. Volumetric flow rate was quantified by collecting the solution coming out from the outlet at a certain duration of time.

4. Conclusion

Microfluidic system with square-qave design to represent arteries equipped with peristaltic pump has been fabricated. Increasing viscosity evidently decreases fluid debit flow hence slowing down the volumetric flow rate. Wax situated at the channel decreases flow rate, however diluted fluid can exhibit faster flow eventhough wax is present. Diluted 1,3-propanediol (at a viscosity of 1.5 mpas) shows similar volumetric flow rate (when it passes through microfluidic channels with wax) with normal blood viscosity 4,0 mpas (when it passes microfluidic channels without wax). This similarities indicates an increased of blood flow when heparin is added in excess in IAHF method, which induces an improvement of organ motoric function

5. References

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