



Brain Protection Effect of Lidocaine Measured By Interleukin-6 and Phospholipase A2 Concentration in Epidural Haematoma with Moderate Head Injury Patient

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Abstract

The aim of this study is to find out the neuroprotective mechanism of lidocaine in epidural haematoma (EDH) in moderate brain injury. The effects are measured by the level of interleukin-6 (IL-6) and phospholipase A2 (PLA2).

This study is done in forty epidural haematoma patients with moderate brain injury. The objects are divided into two groups, group A with NaCl 0.9% infusion only (control) and group B with NaCl 0.9% infusion combined with lidocaine 1 mg/kg/hr. The blood samples were taken right before induction and two hours after infusion.

The result shows that the level of IL-6 and PLA2 is significantly low in group B ($p < 0.005$) with Mann Whitney and Dependent t test. The decreasing level of IL-6 and PLA2 is related with the dose of lidocaine. The inhibition mechanism of IL-6 and PLA2 secretion by lidocaine is considered as a responsible factor in inflammation and brain cells damage.

Summary

- Infusion of lidocaine 1 mg/kg/hr will decrease the level of IL-6 in moderate brain injury
- Infusion of lidocaine 1 mg/kg/hr will decrease the level of PLA2 in moderate brain injury

Keywords: Moderate brain injury; Lidocaine; IL-6; PLA2

Introduction

Traumatic Brain Injury (TBI) is considered as a daily case. Traumatic Brain Injury is defined as non-degenerative and non-congenital disorder that is caused by an outer mechanical mass. This injury will result in whether temporary or permanent impairment in cognitive or even psychosocial function that will lead to unconsciousness status. TBI cases could be found in many level of emergency [1,2].

Until now there is no adequate standardized pharmacological therapy for primary brain injury. The recent management is just to impede to secondary brain injury that will activate series of ischemic cascades along with pro-inflammation cytokine release and free radicals [3]. In a severe TBI, there is excessive inflammation process and so many pro-inflammation cytokines are released (TNF- α & IL-6) that will lead to cellular apoptosis and necrosis. Many drugs had been proposed as a potent drug in bringing down the permanent neuronal damage, but only few are proven clinically [4].

Lidocaine is now used as an adjuvant neuroanesthesia with neuro protect effect. The clinical effects of lidocaine are determined by the dose. When given after isoelectric electroencephalograph induced by Pentothal, lidocain can reduce the Cerebral Metabolic Rate for Oxygen (CMRO₂) from 15-20%. The clinical recommended dose is 1,5 mg/kg [5]. The using of lidocaine also blunts the hemodynamic response for intubation. Generally lidocaine has been used to inhibit the increasing blood pressure by laryngoscope during intubation [5-8].

Lidocaine infusion intravenously has been used in post-operative pain management [9-11]. Joad et al. (2002) used the infusion of intravenous lignocaine in diabetic neuropathic pain management and in cancer pain. Lidocaines were given intravenously 5 mg/kg during 60 minutes in normal saline 1 mg/kg. Previous study had showed

that using 2 mg/kg lidocaine during 40 minutes is quite effective in pain management. During infusion no significant side effects (tremor, tinnitus, dizziness, convulsion, respiration disorder, bradycardia and hypotension) were reported [12].

Intravenous lidocaine had been recognized for its brain protective effect through inhibit sodium channel, repairing depolarization and reduce sodium influx. In animal experiment, lidocaine can reduce the size of infarct tissue and repair the neurological deficit in a focal cerebral ischemia. Lidocaine works through inhibition of apoptotic pathway in penumbra. The late administration of lidocaine 45 minutes after focal cerebral ischemia onset still point out some neuronal repairmen either in nuclei and penumbra [5,13,14].

In low dose, lidocaine has anticonvulsant effect and works satisfying in epileptic state management. Intravenous lidocaine will be considered harmful if the level in plasma increasing significantly. In toxic condition, lidocaine will lead to seizure [5]. Until now the local anesthetic therapy and its correlation with neuroapoptosis is still undetermined [15,16].

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Brain injury has been known as independent risk factor for complication in patient with multiple trauma. It is reported that on 40% patients with TBI show clinical signs of pneumonia. TBI is also related with several cytokines i.e. interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin 8 (IL-8) and interleukin-10 (IL-10) in cerebrospinal fluid. It is important to know that the advanced level of pro-inflammation cytokines and intracranial pressure can cause neuroimmune pathway activation [17,18].

Pro-inflammatory and anti-inflammation cytokines level in a severe injury show possibility to cause systemic immunological change. This condition is considered as balancing mechanism from the cytokines that appear as clinical sign in patients [19,20].

The other study show that the excess production of pro-inflammation and anti-inflammation cytokine mediator will lead to multiple organs dysfunction. Major pro-inflammation cytokines in injury and surgery are TNF- α , IL-1 β , IL-6 and IL-8 [21-23]. Every cell death in TBI will have phospholipid membrane hydrolysis through the group of Calcium Independent VIA Phospholipase A2 (iPLA2-VIA). They found that iPLA2-VIA also form lysophosphatidilcholine in apoptotic cells U937 in clearance efficiency by macrophage [24].

Another phospholipase study (Jangi et al., 2005), shows that cell death is determined by phospholipase C that release by antagonist histamine H₁ through calcium homeostasis modulation of malign melanoma in human [25]. Phospholipase A2 causes destruction of phospholipid membrane in neuron cell death. Phospholipase A2 is a lipolytic enzyme that hydrolyze acyl bond on Sn-2 position from glycerophospholipid. These products are precursor from Platelet Activating Factor (PAF) and eicosanoid that take a major role in inflammation and tissue injury [26].

All pro and controversial for neuroprotective agent, and even real mechanism of lidocaine in Traumatic Brain Injury is our base interested to investigate in this research.

This research was conducted without violating ethics, for the reasons mentioned below:

- Lidocaine given samples did not harm the patient because the drug is often used in the field of neurosurgery and general neuroanesthesia as one of brain protection agents and sympathetic response reducer.
- Patients were given anesthetic and analgesic drugs which are also routinely used in anesthetic actions.
- The study was conducted after obtaining approval from the ethics committee.
- This research was performed after obtaining agreement from the family of the patients before undergoing surgery. Researchers provided detail explanation to the patients' family concerning the procedures to be performed as well as possible side effects that may occur and the precaution that had been prepared by the researchers. After the family fully understood and consented, patients were taken to the operating room to undergo the procedure prescribed.

Subject and Methodology

This study is clinical experimental i.e. human experiment in consecutive way; we input all the sample data from the patient fulfilling the inclusive criteria in emergency neurosurgery. The samples were divided with table random sampling. Sample limitation is based on clinical assessment; before and after treatment we make a laboratory examination through peripheral blood plasma to find out IL-6,

phospholipase and lidocaine level in blood. This study is done in Prof. Kandou Manado Hospital. Sampling and data were collected during January 2012-January 2013. The examination on IL-6 level in peripheral blood is very important as main mediator; initializing the inflammation & metabolic response of injury. IL-6 level is very specific, its level will rise in brain injury and also this will induce free radical, arachnidan acid and molecular adhesion level in secondary brain injury. PLA2 is an enzyme that is activated through excessive glutamate release that will increase the level of intracellular calcium. This condition will induce series of ischemic cascade likewise peroxidase lipids, proteolysis, free radicals and DNA damage that will lead to neuronal cell damage.

Inclusion criteria

- Age 17-55 years old
- Physical state ASA I and II
- TBI period not more than 48 hours
- Patient without pro-coagulant therapy

Exclusion criteria

- TBI patient with worsen condition (unconsciousness and cerebral herniation signs) during observation
- Certain condition that require additional drugs intervention that will interact with the current treatment during observation
- Family's refusal

Drop out criteria

- TBI patient with complication during intervention
- Prolonged ongoing craniotomy procedure (>3 hours)

Data for normal population distribution were processed and analyzed by using statistical Dependent T-Test for numerical scale independent variables which are lidocaine levels in plasma, levels of IL-6, and phospholipase levels; however Mann Whitney test were used for data of uneven population distribution. For categorical variables were evaluated by using Chi-squared test.

With random sample distribution method, the writers expect to get the demographical characteristic and clinical subject distributed within two groups. This will eliminate confusion in comparing expected effect on both groups.

Before intervention, all patients were given oxygen via cannula 3L/min one hour before induction. The subjects were divided into two groups: control group (NaCl 0.9% infusion without lidocaine) and lidocaine group (NaCl 0.9% infusion with lidocaine). Each patient was induced with phentanyl 2 μ g/kg and propofol 2 mg/kg. Intubation was facilitated with rocuronium 0.9 mg/kg. The lidocaine group were given full injection of lidocaine 1 mg/kg before induction, and after induction the patients were given lidocaine infusion 1 mg/kg/hr via syringe pump. This infusion continued for two hours. The control groups were firstly given full injection of lidocaine 1 mg/kg and after intubation we continue with NaCl 0.9% infusion via syringe pump. We use isoflurane and propofol titration (syringe pump) 1-2 mg/kg for maintenance. Anesthetic inhalations with isoflurane were given not more than 1.5 MAC (2% volume). Muscle relaxants were given every 20 minutes continued with 10 mg rocuronium bolus intravenously.

During intervention we observe GCS, blood pressure, heart rate, respiration rate, peripheral saturation (SpO₂), core body temperature

and blood sugar level. After intubation the patient was connected with anesthetic machine with tidal volume 7 ml/kg, respiration rate 12 x/min, inhalation of O₂:N₂O=3 ml:3 ml and isoflurane 2% volume with propofol titration via syringe pump 1-2 mg/kg.

Biomarker IL-6 and PLA2 were examined from peripheral blood sample firstly before induction and two hours after infusion. Each sample was compared by its own before and after intervention. The tendency of IL-6 and PLA2 rising level were compared within two groups. GCS assessment carried out right before entering operation room and 24 hour after surgery. There are no monitoring for intracranial pressure, BIS and evoked potential because of absence in equipment.

The writer use dependent-test in normal population spread i.e. level of lidocaine, IL-6 and phospholipase in plasma. For abnormal population spread the writer use Mann Whitney test. In categorical variable we are use chi square test.

Results

The homogeneity test results of demographic and clinical characteristics of subjects in both groups can be seen in Table 1.

Table 1 shows that both groups can be considered homogeneous for age, initial GCS, the volume of EDH, EDH location, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), HR (Heart Rate), temperature, BS (Fasting Blood Sugar), hematocrit, haemoglobin, leukocytes, platelets, serum Na⁺ and K⁺ serum.

The treatment group is the group that gained in the lidocaine infusion fluids 0.9% NaCl and the control group only received 0.9% NaCl infusions without lidocaine. 2 hours post infusion, serum lidocaine levels examined in both groups. Comparison of serum lidocaine levels between the two groups were tested with independent sample test. The result can be seen in Table 2.

Variable	Group		Independent Sample t test
	Lidocaine Infusion (n=20)	Control (n=20)	
Age (yrs)	30.4 ± 10.0	30.3 ± 10.4	p=0.963
GCS in admission	10.1 ± 0.6	10.1 ± 0.8	p=0.832
EDH volume (ml)	7.78 ± 4.99	6.05 ± 4.00	p=0.165*
SBP (mmHg)	131.5 ± 7.7	131.5 ± 8.4	p=0.984
DBP (mmHg)	79.7 ± 12.2	79.6 ± 12.5	p=0.969
HR (x/ment)	92.8 ± 5.7	94.1 ± 7.0	p=0.522
MAP	114.10 ± 8.53	114.05 ± 9.22	p=0.986
Temperature (oC)	36.8 ± 0.4	36.7 ± 0.5	p=0.442
BS (mg/dL)	94.9 ± 13.5	95.0 ± 13.9	p=0.991
Hematocrit (%)	34.6 ± 3.8	35.7 ± 3.4	p=0.360
Haemoglobin (gr%)	11.7 ± 1.4	11.8 ± 1.2	p=0.878
Leukocyte	9455.0 ± 2815.5	9445.0 ± 2832.2	p=0.991*
Trombocyte	245.9 ± 91.3	240.3 ± 90.7	p=0.854
Na ⁺	138.7 ± 2.9	138.8 ± 3.3	p=0.881
K ⁺	3.3 ± 0.2	3.3 ± 0.3	p=0.954
EDH location	n	n	p=0.896**
L1	10	10	
L2	3	4	
L3	7	6	

*Mann Whitney U test; **Chi-Square test; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; BS=blood sugar L1=Parietal/Frontoparietal/temporoparietal, L2=frontal/oksipital, L3=temporo/frontotemporal

Table 1: Demographic and clinical characteristics of subject in both groups.

Lidocaine Serum (ng/ml)	Group		Independent Sample t test
	Lidocaine Infusion (n=20)	Control (n=20)	
Mean ± SD	1901.7 ± 169.6	171.9 ± 75.8	
Minimal/Maximal	1776-2514	68-388	p=0.000

Table 2: The comparison of serum lidocaine levels between NaCl 0.9% infusion groups (control) and NaCl 0.9%+Lidocaine group.

Groups	(Mean ± SD) PLA2 serum Concentration (ng/ml)			Paired t test
	Before Induction of Anesthesia	After 2 hour giving infusion	Changes Significancy	
Control (n=20)	(18.90 ± 5.59) ^a	(20.20 ± 5.27) ^a	Increase (1.3) ^a	p=0.483
Lidocaine (n=20)	(19.00 ± 3.70) ^a	(10.00 ± 1.75) ^a	Decrease (9.0) ^b	p=0.000

Superscript shows not significant different with Mann Whitney (p>0.05) if different, show significant different with Mann Whitney (p<0.05).

Table 3: The comparison of PLA2 serum concentration between two groups.

Table 2 shows that serum lidocaine levels 2 hours after the infusion was higher in the treatment group (1901.7 ± 169.6) ng/ml than the control group (171.9 ± 75.8) ng/ml. Results of independent t test showed no significant differences (p<0.05).

Changes in serum PLA2 levels before induction and 2 hours post infusion in the control and treatment groups were tested by paired t test. Comparison of serum PLA2 levels between the two groups before surgery, and so is the ratio of serum PLA2 levels 2 hours post infusion and comparison of changes in serum PLA2 levels before induction until after 2 hours of infusion between the two groups was tested by Mann Whitney test. The result can be seen in Table 3.

Table 3 shows that in the control group there was an increase in serum PLA2 levels of 1.3 ng/ml of (18.90 ± 5.59) ng/ml to (20.20 ± 5.27) ng/ml, but the results of paired t test showed no significant changes (p>0.05), whereas in the treatment group decreased serum PLA2 levels of 9.0 ng/ml of (19.00 ± 3.70) ng/ml to (10.00 ± 1.75) ng/ml and significantly (p<0.05). Results of Mann Whitney test serum PLA2 levels between the two groups before surgery showed no significant difference (p>0.05), but after 2 hours of infusion was significantly different (p<0.05), as well as comparison of changes in serum PLA2 levels, significantly different (p<0.05) between the two group. Thus, changes in serum PLA2 levels significantly different between the two groups. In the treatment group decreased, whereas the control group did not change.

Figure 1 show that the serum PLA2 levels before the induction of the same (coincident) in both groups, and after 2 hours of infusion, serum PLA2 levels decreased in the treatment group, whereas the control group remained at or slightly increased.

Changes in serum levels of IL-6 in the control group and the treatment before induction and after 2 hours of infusion were tested with the Wilcoxon test. Comparison of serum levels of IL-6 between the two groups, and so did 2 hours after the infusion and comparison of changes in serum levels of IL-6 before induction until 2 hours after the infusion between the two groups was tested by Mann Whitney test. The result can be seen in Table 4.

Table 4 shows that in the control group increased serum levels of IL-6 at 7:20 pg/ml of (48.60 ± 30.52) pg/ml to (55.80 ± 32.95) pg/ml, but the results of the Wilcoxon test showed no significant changes (P>0.05), whereas in the group treated serum levels of IL-6 decreased by 24.10 pg/ml of (43.70 ± 24.72) pg/ml to (19.60 ± 11.27) pg/ml and

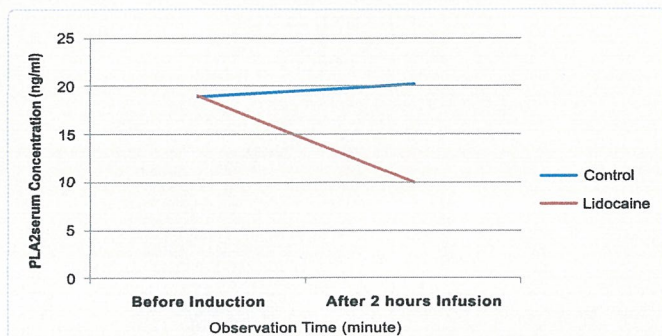


Figure 1: The comparison of PLA2 serum concentration changes before induction until 2 hours giving infusion between two groups.

Groups	(Mean ± SD) kadar IL-6 serum (pg/ml)			Wilcoxon test
	Before Induction of anesthesia	After 2 hours Giving Infusion	Changes	
Control (n=20)	(48.60 ± 30.52) ^a	(55.80 ± 32.95) ^a	Increase (7.20) ^a	p=0.505
Lidocaine (n=20)	(43.70 ± 24.72) ^a	(19.60 ± 11.27) ^a	Decrease (24.10) ^b	p=0.000

Superscript not different in same column shows Mann Whitney results not significant different ($p > 0.05$) and if different, shows Mann Whitney significant different ($p < 0.05$).

Table 4: The comparison of IL-6 serum concentration changes between two groups.

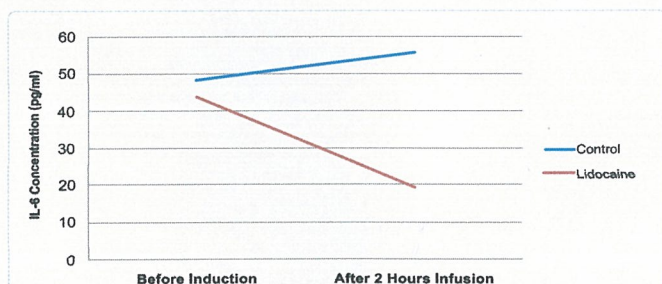


Figure 2: The comparison of IL-6 serum concentration changes before induction until 2 hours after infusion between two groups.

significantly ($p < 0.05$). Results of Mann Whitney test serum levels of IL-6 between the two groups before induction showed no significant difference ($p > 0.05$), but after 2 hours of infusion was significantly different ($p < 0.05$), as well as comparison of changes in serum levels of IL-6 between the two groups, significantly different ($p < 0.05$). Thus, changes in the levels of serum IL-6 was significantly different between the two groups. In the treatment group decreased, whereas the control group did not change.

Figure 2 shows that the levels of serum IL-6 was slightly higher in the control group before induction, and after 2 hours of infusion serum levels of IL-6 decreased in the treatment group, whereas the control group slightly increased.

When tested the correlation between levels of lidocaine with HR, TDS, TDD, levels of IL-6, and serum PLA2 levels after extubation, the results can be seen in Table 5.

Table 5 shows a strong negative linear correlation and significant ($p < 0.05$) between lidocaine with HR, SBP, DBP, levels of IL-6, serum PLA2. The higher levels of lidocaine, the lower HR, SBP, DBP, serum levels of IL-6 and serum PLA2.

To assess the side effects that may occur is observed on cardiovascular responses (heart rate and mean arterial pressure). The results of the analysis can be seen in Table 6.

Table 6 shows that there were no side effects such as bradycardia, hypotension both the control group and the treatment group.

Discussion

General data of patients included age, height, weight, BMI, initial systolic pressure, diastolic pressure early, average blood pressure, respiratory rate, pulse rate, SPO₂, core temperature, blood sugar level, and GCS showed no significant differences between the two groups, which means the two groups are relatively homogeneous.

The average patient age was 30 years, mean trauma effect would be the same as his GCS score was the same. In contrast to when one group more than 60 years old. Although the severity of the primary injury similar but different because brain tissue therapeutic effect will be different then.

Effects of decreased Interleukin-6

Interleukin-6 is a cytokine that is produced by many types of cells, including activated by mononuclear phagocytes, endothelial cells, and fibroblasts, which serves both as the initial immunity (innate immunity) as well as adaptive immunity (adaptive immunity). Interleukin-6 stimulates the synthesis of acute phase proteins by hepatocyte-hepatocyte growth as antibodies produced by B lymphocytes [27].

Interleukin-6 produced in response to the presence of microbes and for other cytokines, particularly IL-1 and TNF. Interleukin-6 is also formed by some activated T cells. Functional form of IL-6 is a homodimer, with each subunit forming globular four field- α -helix (α -helical four-globular). IL-6 receptor is composed of a protein and a subunit bound cytokine signal conductors, which are both part of a derivative type I cytokine receptor main signaling pathways induced by IL-6 include activation of Jak 1 and STAT3, and tends to cause the transcription of various types Different genes [27].

Interleukin-6 has a variety of different actions. In innate immunity, IL-6 stimulates the synthesis of acute phase proteins by hepatocytes and subsequently participated in the acute phase response. IL-6 stimulates the production of neutrophils from bone marrow progenitors, usually acting together with the group stimulating factors. In adaptive immunity, IL-6 stimulates the growth of B lymphocytes differentiate

Variable	Serum Lidocaine	
	Coefficient Correlation (r)	Significance (p)
HR	r=-0.701	p=0.000
SBP	r=-0.823	p=0.000
DBP	r=-0.788	p=0.000
IL-6 serum Concentration	r=-0.677	p=0.000
PLA2 serum Concentration	r=-0.734	p=0.000

Table 5: The correlation between lidocaine concentration with IL-6 and PLA2 serum concentration, HR, SBP and DBP after giving 2 hours infusion.

Observation Time	Minimal-maximal Heart Rate (times/minute)		Minimal-Maksimal MAP (mmHg)	
	Control	Lidocaine	Control	Lidocaine
Before Induction	78-105	78-102	96-127	97-130
After 60' Infusion	78-102	70-92	114-130	78-113
After 120' Infusion	78-100	68-90	109-132	77-114

Table 6: Distribution range of heart rate and mean arterial pressure between two groups.

into antibody-forming antibodies. Interleukin-6 as a growth factor effect on neoplastic plasma cells (myeloma), in most myeloma cells, autonomous secretion of IL-6 as a growth factor. Interleukin-6 can trigger the growth of hybridomas produce monoclonal antibodies. Interleukin-6 trigger an immune response through the production of several proinflammatory cytokines, inhibits the formation and action of regulatory T cells [27].

The results of this study showed that administration of lidocaine infusion of 1 mg/kg/hour for 2 hours showed higher levels of IL-6 are smaller due to decreased production of IL-6 were significantly compared with the control group who were not given lidocaine. Lidocaine is a compound that is able to block Na⁺ channels and Ca²⁺. Blockade of Na⁺ channels by lidocaine will cause Na⁺ can not enter the cells so that the cell death caused by lysis of the cell membrane will be reduced, so that the production of IL-6 by macrophage reduced due to reduction in macrophages in charge of cleaning up dead cells (apoptosis).

Sodium is one of the three major ions (K⁺, Na⁺, Cl⁻) that regulate membrane potential. From the literature it is reported that some other ions such as PO₄²⁻, Ca²⁺, SO₄²⁻, and Mg²⁺ (Ca²⁺ except in certain circumstances no effect) does not affect the change in membrane potential. In the resting state action potentials in neurons molecule is -50 to -70 mV. Besides "resting ion channels" on the membrane, there is also the type of channel for ions Na⁺ and K⁺ are called Voltage-gated channels. In the resting state, Voltage-gated channels closed, no ions are transported, but if the area is polarized, the canal opened in a short time ago ions Na⁺ or K⁺ flowing through it [28].

Each channel for ion transport pathways in the cell membrane of neurons can only be passed by a certain ion. In the resting state no stimulation of cells so that the cell membrane potential in a state of rest. In the circumstances that led to the opening of voltage-gated channels (usually very fast) changes in membrane potential and this is what causes the onset of electrical signals called action membrane potential. There are two types of channels in addition to the channels above, which can open and close. Channels that provide answers to the existence of chemical signals responsible for the formation of an electrical signal, called a ligand-gated channels. This channel opens when there is stimulation of extracellular molecules. Some are some channels that respond to molecules in the cell, for example, to a molecular "second messengers" such as Ca²⁺ or other molecules such as cyclic GMP, and G protein subunits that are activated by cell surface receptors. Is a cycle of action potential depolarization, hyperpolarization and returned to the resting state. Specifically electrical changes caused by Na⁺ channels and voltage-gated K⁺ that open and close in response to changes in membrane potential.

Electrical stimulation in a process cell transmission in this brain neuronal cells, preceded by electrical stimulation (impulses) and ends with a new impulse terbangkitnya on post-synaptic nerve cell membranes. Electrical stimulation through the nerve fibers (axons) will generate impulses that propagate along the axon to its end. Impulse propagation in axons takes place by the mechanism of opening and closing gates Na⁺ ion channels in the membrane of axons. Impulse arrives at the end of the axon, which is home to the neuromuscular relationship, will open the gates of Ca²⁺ ion channels regulated by changes in electrical voltage. With the opening of the ion channel gate of the Ca²⁺, Ca²⁺ ions enter into the tip of the axon, followed by the release of acetylcholine (neurotransmitter) with exocytosis mechanism.

Ca²⁺ channels gate opening in response to membrane depolarization (with the arrival of impulses) is very similar to the opening of the gates

of the Na⁺ ions. The opening between the two modes is revealed that there are two important differences: first: the ion channel gate for Ca²⁺ only for Ca²⁺, unlike other gates, and two: the opening of the gates last for no depolarization, because it is not immediately inactivated. Depolarization of the axon membrane is a change in the electrical charge on both sides of the membrane surface resulting in the presence of nerve impulses [29].

Ca²⁺ ion channels gate at most a limited presence in the membrane of axons presynapsis, although sometimes there is very little. Although Ca²⁺ ions that enter very little, but have an important effect. Entry of Ca²⁺ ions after the opening of the channel gate due to differences in the levels of Ca²⁺ ions are sharply between extracellular concentration (10⁻³ M) with Ca²⁺ ion concentration in the cytosol-free at the end of the axon (10⁻⁷ M). With the influx of Ca²⁺ ions into the cytosol would lead to higher levels of Ca²⁺ ions, but only lasted a short time. Free Ca²⁺ ions rapidly bound by the binding protein, taken by special bubbles and mitochondria, so that the levels of Ca²⁺ ions in the cytosol decreased again. At current levels of Ca²⁺ ions in the cytosol of the axon tip increases, the bubbles synaptic membranes containing neurotransmitter presynapsis will stick close to the membrane, followed by the release of their contents into the synaptic cleft. The number of bubbles that release their contents increasing with increasing levels of Ca²⁺ ions.

The above mechanism requires a deep understanding of the parts of cells that were actively involved in the cellular process that is closely related to the ischemic cascade that occurs in a traumatic brain injury. One of them with regard to the function of mitochondria as one of membranous organelles in the cytoplasm of cells that are active in the process of cell metabolism. With electron microscopy shows that the mitochondria have double walls, each of which is structured lipids dwilapis. Wall next to the folded form partitions called cristae mitochondriales. Mitochondrial about 0.35-0.74 microns diameter. In the mitochondria are more dense fluid from the cytoplasm called the mitochondrial matrix. In this matrix contained in a grain called matrix grains of 30-50 nm.

In the presence of molecules found in mitochondria strands of DNA, RNA, and ribosomes are slightly different from those contained in the cell cytoplasm. Because of the presence of DNA, RNA, and ribosomes of its own, mitochondria are able to make its own proteins. In the absence of visible cells is the formation of new mitochondria results in mitochondrial fission amitosis. The existence of the division's ability and the ability of the protein mensesintesis independently, the mitochondria are said to be semi-autonomous.

Mitochondria have their own limitations to mensesintesis membrane phospholipids. If other membranous organelles are getting protein and lipid membrane by means of the addition through the membrane vesicles from the ER, the mitochondria get these materials does not in this way. Protein and lipid separately accepted, even protein can be obtained from the synthesis itself.

In the process of carbohydrate metabolism in a cell, there was a successive anaerobic and aerobic reactions that require oxygen. At first the carbohydrates absorbed by the cells will be broken with the help of some anaerobic enzymes so there pyruvic acid. The process of change in either acetic acid derived from the breakdown of carbohydrates and fats takes place in the mitochondria and will undergo an aerobic process in the Krebs cycle. This latter process is called cellular respiration.

Lysosomes as one of membranous organelles in the cytoplasm also needs to be understood in a bubble because there lysosome enzymes

protease hydrolysis eg, glycosidases, lipases, phospholipases, and phosphatases. Lysosome function to digestive substances that can not be described or bacteria that have difagositosis by these cells. Phagocytes that families who are able to remove the unwanted cells, such as granulocytes, monocytes, and macrophages that contain lots of bubbles lysosomes. After difagositosis particles initially enveloped by the plasma membrane as a bubble called the phagosome. When the parts of cells that are still alive, like organelanya is not working anymore, it becomes necessary parts of the destroyed cells. Necessary to destroy the enzymes stored in lysosomes.

After cell death, usually will lyse parts because they contain enzymes contained in the lysosomes become free by the destruction that enveloped membrane. It is probable that act on a series of ischemic cascade that occurs after primary and secondary brain injury, where one product is released phospholipase enzyme that apparently formed as a result of damage to the structure of physiological and structural membranes that envelop, in this case is closely related to impaired charge ions across the cell membrane due to the influx of Na^+ influx followed by Ca^{2+} as a series of apoptosis and necrosis cascade in primary and secondary brain injury [5].

A chemical signal is delivered from outside the cell through a receptor on the cell surface, and then delivered to the cell nucleus. This process is very complex as it involves a variety of chemical and physical properties of signaling proteins, which others do not because of changes in the electrical charge on the protein molecule [28]. At some tissue damage will occur inflammatory process characterized by increased proinflammatory cytokines IL-1B, IL-6, TNF. Effects of lidocaine which reduce cell death caused by the Na^+ channels of barriers will lead to reduced inflamasi process.

Interleukin-6 is a proinflammatory mediator molecule, which is one of the paracrine function of neuronal cells in the brain to produce something this proinflamasi. Dimana mediator function of the mediator is to give special signals to the target cells in the surrounding areas, so to reach the target cells does not require special freight. Mediators are classified in this category, usually unstable, quickly broken, and it was quickly accepted by the target cells. But do not rule out the possibility that these mediators can be found in the blood circulation. The interests of these mediators is very broad, because it depends on several things, which depends on the type of mediator-producing cells, the target cells, and types of mediators are released. Each of these factors can be different from each other. There are so many mediators in the communication system, so that the use of specific terms, ie cytokines. So many mediators are included in cytokines, so do the grouping based on the producer cells, and for interleukins in this case are discussed in this study that IL-6, including chemokines, namely mediator function in the migration of inflammatory cells.

Lidocaine that inhibit Na^+ channels, followed by Ca^{2+} channel inhibition that Ca^{2+} is not going to get into the mitochondria which causes inhibition of cell damage that is more than 72 hours later. Both rapid cell death due to the influx of Na^+ or slow due to the influx of Ca^{2+} will end up with the occurrence of specific neuronal cell necrosis characterized by an inflammatory process, where it can be detected from elevated levels of proinflammatory cytokines. Thus the ability of lidocaine to block Na^+ channels, followed by Ca^{2+} channel inhibition is indicated by lower levels of IL-6 in plasma.

Effects of decreased Fosfolipasei A2 (PLA2)

Cytosolic phospholipase A2 (cPLA2) is an enzyme that is important

in fighting mediates arachidonic metabolism which can cause cerebral ischemia which subsequently trigger brain cells to oxidative injury, blood-brain barrier dysfunction, and edema. In a previous study mentioned that the p38 mitogen-activated protein kinase (MAPK) phosphorylation and activation associated with cPLA2 and arachidonic acid release, although the involvement of the p38 MAPK pathway in the activation of cPLA2 and reaktif oxygen species in 38 MAPK/cPLA2 expression after ischemia reperfusion injury in the brain is still not so clear. In that study it was found that the p38 pathway can trigger the occurrence MAPK/cPLA2 disruption of the blood brain barrier with vasogenic edema secondary, and that superoxide anions can stimulate these pathways after ischemic reperfusion injury.

Disruption of the blood brain barrier is an important event during cerebral ischemia that occurs in a series of traumatic brain injury, where there is an influx of Na^+ which will be followed by water influx, and subsequent vasogenic edema and secondary brain injury are closely related to inflammatory processes with products proinflammatory cytokines as indicators of the incident. The blood brain barrier being one of the main targets for understanding the mechanisms that mediate the damage caused by cerebral ischemia.

Arachidonic Acid (AA) causes the blood-brain barrier dysfunction and subsequent brain edema. AA can also be converted into inflammatory lipid mediators, eicosanoids, through the lipoxygenase pathway or Cyclooxygenase (COX), which plays an important role in brain edema. Several studies have shown inhibition of AA metabolism would reduce cerebral ischemia that trigger oxidative injury, blood-brain barrier dysfunction, edema, and infarction of the brain cells [30].

According to research by Casas et al., (2005) who found that exogenous arachidonic acid reduces mitochondrial membrane potential and Ca^{2+} after excessive charge, membrane depolarization decreased significantly in expression cells. Enhanced Green Fluorescent Protein (EGFP) from the cytosolic Group IVA Phospholipase A2 α (CPLA2 α) compared with the normal number of cells the expression of CPLA2 α . This suggests that the initial event of cell death triggered by the amount of Ca^{2+} overload and this can be prevented by high levels of arachidonic acid, which would lead to mitochondrial depolarization [31].

cPLA2 to mediate the metabolism of AA and associated with the production of eicosanoids, such as prostaglandin and leukotriene. cPLA2 metabolism regulated by intracellular Ca^{2+} and translocation from the cytosol to the membrane [30]. It is unclear why the stabilization of the membrane by the Na^+ channel blockade mechanism which will be followed by Ca^{2+} channel blockade as a follow-up mechanism in the ischemic cascade circuit as mentioned in theory, would reduce or inhibit the significant increase of PLA2 as expressed in this research hypothesis.

In addition to a series of necrosis that occurs, Perez et al., found that the H^+ + peroxide as a strong oxidant can cause cell death through apoptosis in various cell types. This cell death results in the hydrolysis of membrane phospholipids by calcium independent group VIA Phospholipase A 2 (iPLA 2-VIA). They found that beyond the direct destructive role in apoptosis, iPLA 2-VIA also contribute to shaping lysophosphatidilcholine in apoptotic U937 cells that contribute to the efficiency of clearance by macrophages [24].

Several other studies of the phospholipase is like that done by Jangi et al. who examined the cell death depending on Phospholipase C is triggered by histamine H1 antagonist via modulation of Ca^{2+} homeostasis in cells of human malignant melanoma cells but not in melanocytes normal [25].

The influx of Ca^{2+} ions will cause massive activation of phospholipase in the cell wall which in turn will lead to the release of free radicals, lipid peroxidation, irreversible damage to the cell membrane, and ends with the death of the cell. Lidocaine is in the upstream mechanisms by blocking Na^+ channels that will diikutidengan inhibition of Ca^{2+} channels, so there is no influx of Ca^{2+} ions into the cell on a massive scale.

In this study artifacts PLA2 significant decrease in the group that received intravenous lidocaine which means there is inhibition of the Na^+ channels, followed by Ca^{2+} channels, resulting in edema, inflammatory reaction, and the product PLA2.

Confounding factors

The factors that are confounding variables did not differ between the lidocaine group and the control group. SpO_2 between the two groups showed no significant difference. Hypoxemia defined as $SpO_2 < 90\%$ will increase morbidity and mortality, and this is not the case in both groups studied. Hyperventilation until Pa_2 less than 30-35 mmHg can rapidly decrease the intracranial pressure is fast, but also can cause and exacerbate cerebral ischemic neurologic outcomes occurred. The decrease intracranial pressure by hyperventilation are temporary and can cause rebound intracranial hypertension due to a decrease in Pa_2 is too fast during the initial hyperventilation [32].

In a traumatic brain injury, it is necessary to maintain oxygenation with SpO_2 targets more than 90%, maintaining hipokarbia normokarbia or mild, normotermia (maintaining a temperature of $37^\circ C$) and fixed normoglikemi. The brain is an obligate glucose users, where hyperglycemia is associated with an increase in cerebral metabolism. Reduction in cerebrospinal fluid are often found in multiple trauma, and shock, then any state of hyperglycemia can lead to increased anaerobic metabolism, pH changes and worsening outcomes.

Core temperature between the two groups showed no significant difference between the two groups. Hyperthermia is defined as body temperature $> 40^\circ C$ and $< 30^\circ C$ will lead to a coma patient. and this is not the case in both groups studied. So at every hypothermia that occurred within 60 minutes after injury and maintained for 48 hours showed some favorable neurologic outcome in patients with severe head injury [33].

Increased body temperature will increase $CMRO_2$ that causes ketidakimbangan between demand and supply of oxygen. Several clinical studies with mild hypothermia for 24-48 hours after severe head injury repair neurological outcome. Temperature setting of patients treated in the ICU is the concept of "low normothermia" 'ie the patient is maintained in a temperature of $36^\circ C$. *In vitro* studies indicate that hypothermia will maintain ATP, reducing the influx of Ca^{2+} , improves electrophysiological recovery from hypoxia. While hyperthermia will spend ATP, increasing the influx of Ca^{2+} and interfere with recovery. The presence of fever in the neuro and cardiac patients will worsen outcome [5].

The temperature must be controlled in all patients, especially in patients with postoperative specific nerves and brain injury. The increase in temperature is associated with an increase in oxygen consumption of the body about 10-12% per degree, which will decrease the amount of oxygen available to the brain. Every effort should be made to prevent a rise in body temperature, but when it occurs should be treated aggressively [34].

Blood pressure showed no significant difference between the two

groups. Hypotension is defined as systolic pressure less than 90 mmHg did not occur in both groups. Hypotension will increase morbidity and mortality. There were no significant differences in blood pressure, pulse rate, temperature, and blood sugar in both treatment groups ($p > 0.05$). So it can be said that this result is actually due to the effect of lidocaine infusion.

Glasgow Coma Scale between the two groups showed no significant difference. Severe head injury is defined as a GCS 3-8 will increase morbidity and mortality, and this is not the case in the two groups under study because the sample restricted to patients with moderate head injury. At hematoma expansion is not immediately controlled, there will be an increase in intracranial pressure that is not controlled preceded by clinical symptoms such lateralization ipsilateral pupillary dilatation due to herniation of the third cranial nerve dysfunction, especially if the patient is not immediate intervention with decompression, may be accompanied by death [33].

Conclusion

From this study it can be concluded that:

- Lidocaine infusion of 1 mg/kg/hour lower levels of IL-6 in the moderate TBI.
- Infusion of lidocaine 1 mg/kg lower levels of PLA2 in moderate TBI.

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