Migraine Abort Therapy Using Neuromuscular Electrical Stimulation, A Study on the Role of NO and Cerebellum in the Migraine Pathophysiology

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Introduction
Oral therapy to abort a migraine ictal slowed in effect because of the absorption problem during ictal. There was an endocannabinoids deficiency on the migraine sufferer. Endocannabinoids suppressed the inflammation of the trigeminal ganglia. This research used Neuromuscular Electrical Stimulation (NMES), based on the fact that the NO and endocannabinoids had pain modulator, related to the cerebellar LTD. Lately, it has known that the cerebellum involved in the cortical spreading depression during ictal.

Method
The research conducted from February 17th, 2010 until 2015 after receiving an approval from the Ethical Committee (February 16th, 2010), which was also given by the Director General of the Correctional Directorate of the Law and Human Rights Ministry, to do a research on the inmates as the subject (October 20th, 2009). Subjects who fulfill the IHS (International Headache Society) criteria, including a migraine with aura and without aura, were randomized into a clinical trial group (n=33) and sham group (n=30). Neuromuscular Electrical Stimulation was performed with blinding. Endogenous exhaled NO level and clinical improvement (VAS) is written down before and after.

Result
There were clinically and statistically significant in the clinical improvement and a change of endogenous exhaled NO level after intervention compared to the sham group.

Conclusion
There was a clinical improvement in using NMES for an abortion migraine ictal.

Keyword: NMES; endocannabinoids; NO; LTD; migraine

Abstract
A migraine is a health problem occurring in the society which has a big impact on the sufferer. Every year, ten million people in the United States suffer from a migraine. Sixteen percent of a population was a migraine sufferer. Migraine sufferers are mostly women (18%) than men (16%). In Surabaya, in 1984, amongst 6,448 new patients at the clinic, 180 were migraine sufferers [1]. At the Cipto Mangunkusumo Hospital, Jakarta, from the 1,298 new patients had come from January to May 1988, 273 of them were migraine sufferers [2]. A population study in Bogor showed that 61% of headaches occurred in the age group of 25-54, 8.6% of this age group suffer from a migraine, with the detail as follows: 81.6% suffers from a migraine without aura, 16.8% suffers a migraine with aura, 0.6% suffers a migraine with complication and 1.2% suffers a cluster headache [2].

A migraine is defined as a chronic interference which has a big impact, usually unilateral, a pain in the head that throb accompanied by aura as a symptom [3]. Migraine sufferer experiences a neurochemistry change inside the dura membrane in the brain, the increase of endogenous exhaled NO level that originated from the excessive iNOS (inducible NOS) activity. The inducible NOS (iNOS) are an enzyme that has proven to increase during an acute migraine ictal, and once it induced, this enzyme can stay in the blood for 4 hours, while eNOs and nNOs don't [4,5]. Some researchers stated that the NO was the case of the pain, while other researchers opposed. Nitric Oxide that causes the pain was the NO donor exogenously, such as GTN (Glyceryl Trinitrate) which could widen the diameter of the blood vessel excessively, so that stimulation to sensory nerve fiber on the wall of the blood vessel [6-9]. The Endogenous NO will also cause pain if a disease process produces NO excessively, for example, when an excessive iNOS activation occurs, it produces NO excessively. Some researchers proved that the endogenous NO could become an antinociceptive, but if too much, NO can also act in hyperalgesia and allodynia [4,8,10-13]. The advancement in migraine therapy will improve the human life quality and decrease the amount of pain and also the attendance list of workers [14].

All these times, migraine diagnosis has only based on the International Headache Society criteria subjectively. There is not yet an objective parameter, such as a laboratory test, which can
The researchers tend to measure the iNOS level inside the blood and endogenous exhaled NO which is related to acute a migraine ictal. The measuring of iNOS level in the blood during an acute migraine ictal was not practical because a radioactive laboratory test is needed [18].

The measuring of the NO in the blood as a picture of the iNOS activity had proven to be incorrect due to its instability because nitrate could be a result of a germ metabolism inside the intestine [10].

The measuring of Endogenous exhaled NO level of the migraine sufferer was not painful and easy to do. The endogenous exhaled NO analyzer/equipment has available in many forms and has been validated and recommended by the American Thoracic Society [19]. This test expected to be able to be used as a more objective migraine diagnosis in the future based on the diagnostic study [15-17].

The research showed the pattern of endogenous exhaled NO level on the migraine sufferer which has never been done in Indonesia. Until today, there has only one research that measured the endogenous exhaled NO level on the migraine sufferer using an exhaled NO analyzer/equipment which had been done by Van der Schueren and colleagues, who want to prove that there was an increase on the endogenous exhaled NO level during an acute migraine ictal. This research achieved an average point of the endogenous NO level during a migraine ictal, inter-ictal and normal people. The measurement is done in 2-48 hours from an acute migraine ictal and has not yet proven any significant result [5].

Migraine therapy includes pharmacological and non-pharmacological therapy. Pharmacological therapy has a weakness in medicine side effects; drowsiness, balance problem, and the need to monitor the function of the liver and kidney [4,5,17,20,21]. Oral pharmacological therapy to abort a migraine ictal was slow in effect because an absorption problem occurs due to the increase of the sympathetic nerve activity. The research on migraine pharmacological therapy includes interventions on some system that are related to the migraine pathophysiology, such are CGRP, glutaminergic system, serotonergic and endocannabinoids [17,20,22,23].

Until today, there has no higher level of evidence-based medicine for a migraine non-pharmacological therapy. The research on migraine non-pharmacological emphasizes on the natural analgesic which is known as the endocannabinoids. The intervention of the endocannabinoids system can be done pharmacologically and non-pharmacologically. The non-pharmacological intervention enables to reduce the risk of the research subjects. Endocannabinoids are known to be able to suppress the inflammatory process on the ganglion trigeminal by lowering the CGRP and serotonin activities [10]. An endocannabinoids deficiency is known to occur on the migraine sufferer [24,25].

This research uses an electrical stimulation, based on the fact that the NO is the modulator of various neurotransmitter and natural analgesic inside the brain, including endocannabinoids, by the fast type II and III conduction stimulation on the nerve fiber, in relation to the cerebellum activity before a muscle twitch occurs [2, 6, 11, 15, 26-36]. In the last ten years, it is known that the cerebellum is not an organ that only functions in balance. It has been proven that the nerve median stimulation, with the electrical stimulation of 4 Hz and a wavelength of 0,2m/second, can activate the climbing cerebellum fiber [37]. It has been proven in rats, that the climbing cerebellum fiber can be activated with an electrical stimulation, followed by the vasodilatation of the blood vessel around the cerebellum, as a result of the active nNOS, and then followed by the increase of the NO that diffuses into the blood vessel [38]. It has been known that the cerebellum is the main producer of nNOS in the brain [37-39].

Based on the SPECT study, the cerebellum is known to be able to act as an initiator of the cortical spreading depression and can influence the thalamus through the posterior circulation (vertebrobasilar system) [30]. Based on this research, there is a possibility that the endogenous NO can impede the cortical spreading depression so that a migraine ictal can be impeded [40]. The increase of endocannabinoids level of the migraine sufferer, which originated from the increase of the NO endogen that comes from a surgically secreted nNOS (cerebellar NOS) in the LTD process, is expected to be able to suppress the CGRP activity [10]. The facts above is a basic thought which tries to prove that electrical stimulation can be used as one of the abortive therapy during a migraine ictal.

**Method**

This clinical trial research using randomization with blinding. The research took place in the Pondok Bambu women and children state prison, East Jakarta. The research conducted from February 17th, 2010 until 2015 after receiving an approval from the Ethical Committee (February 16th, 2010), which was also given by the Director General of the Correctional Directorate of the Law and Human Rights Ministry, to do a research on the inmates as the subject (October 20th, 2009). Subjects who fulfill the IHS (International Headache Society) criteria, including a migraine with aura and without aura, were randomized into a clinical trial group (n=33) and sham group (n=30). Neuromuscular Electrical Stimulation was performed with blinding. Endogenous exhaled NO level and clinical improvement (VAS) is written down before and after. A validation equipment and measurement had been done in accordance with American Thoracic Association guidance. The population was all migraine patients who come to the nerve clinic at the Cipinang Hospital, Jakarta, the Cipinang Penitentiary clinic, The Pondok Bambu, Salemba, Tangerang, and Bekasi State Prison, and also private practices. The sample population was all migraine patients appropriate with the inclusion criteria. The inclusion criteria were migraine patients with and without aura according to the IHS (International Headache Society) criteria, the age range of 19-55, with the educational background of high school, male or female who are willing to participate in the research. On the
amnesia, physical checkup, and neurological were in a normal condition.

All samples were given explanations about the purpose, procedure, and benefit of the research. If they understood and agreed to participate in the research, they were asked to sign the research permit. The research samples were the migraine patients that fulfill the inclusion criteria and a simple random sampling was used by using lottery paper.

According to IHS (International Headache Society), the subjects that fulfill the criteria of a migraine with and without aura must be randomized into group allocation (experimental and sham). One of the sham groups was the migraine group that uses the medicinal abortive therapy by using sham that was the NMES equipment put on, but not electrically. The electrode puts in the hands of the patients. The NMES machine and monitor, but the patients don’t know the numbers and information on the NMES monitor. The patients thought that the low electrical current might not be felt by them. Only the data collecting staffs were known about subject grouping, while the research staff who measures and do therapy didn’t know about subjects grouping. The researchers did migraine diagnosis but didn’t know which group the patients belong to.

The patients who suffered from a migraine lay down in a peaceful room; a VAS measurement and early NOS androgen exhalation are done. NMES electrode was put in the palm of the hands where the median nerve motoric exist until a muscle twitch on the abductor policies brevis muscle occurs. 30 minutes intervention is followed by measuring the endogenous exhaled NO level 10 seconds after the stimulation ended, in accordance with the American Thoracic Society’s procedure [19]. NMES intervention on the skin surface of the abductor policies brevis muscle on both hands, in accordance with the motoric distribution of the median nerve, until a muscle twitch occurs (a twitch of the muscle caused by the electrical stimulation that influences the motoric nerve), on the frequency and amplitude in accordance with the previous study, which could decrease the migraine pain based on the VAS scale and the endogenous exhaled NO level and also comfortable for the research subjects. The measurement of the endogenous exhaled NO is written down for 10 seconds after the stimulation ended. In every clinical test, the pain degree on the VAS scale is written down, before and after the stimulation on the migraine sufferer on the clinical trial group and sham group.

A quality control by examining it as a whole and also reducing the input vector (man, money, material and method) was done. A picking test had done to see the adherence to the research procedure and reducing the research results. Research data are written on the forms. After going through the editing and coding process, research data recorded in the magnetic disc to undergo a cleaning process. A comparison was done to the sham group and clinical trial on the VAS scale and endogenous exhaled NO level with a t-test or Mann-Whitney test.

Result
The plot of a clinical trial is shown in the Figure 1. Based on Table 1, there was comparable between sham group and clinical trial. Based on Table 2, there was a significant result between clinical trial group compared to the sham group in the endogenous exhaled NO level and VAS.

Discussion
All patients who are willing to become research subjects were given medicinally therapy directly and followed the research procedure in less than 30 minutes after a migraine ictal. The patients were still given the standard migraine therapy procedure in the form of 1000 mg paracetamol on the clinical trial and sham groups.

Information validity of this research is guaranteed, there is a clear definition of migraine diagnosis equipment, and materials used in the research, also the inclusion and exclusion criteria in operational definitions. The subjects understood that this research used an electrical stimulation instead of medicine/chemical substance. The subjects also knew that if a pain occurs caused by the electrical stimulation, it will be taken care of by medical staffs.

The subject recruitment process is done by giving open notification and explanation about the symptoms and signs of migraine pain that are similar to a migraine, and also the purpose, benefit, and contribution to the medical field. Then, registration was done for those who have migraine symptoms and willing to participate in the research. On the third research, exclusion like on the first research is not done. Research participants signed a letter of approval, but before that their rights to quit and the benefit for them was explained. Participants who decided not to continue their participation in the research will still get their medical treatment according to their diseases.

In this, the clinical trial, 170 people who were migraine sufferer were willing to participate in the research. After anamnesis and checkup were done, it was found out that 30 people were a mixed migraine sufferer or a mixed migraine and tension-type headache, so they were not included in the research. 140 people were randomized by using a lottery. The randomization process was done by the third party who is not involved as the research staff, and the result was not shown to the main researcher until the end of the research. The main researcher and the measuring staff didn’t know which group the participants belong to, whether it was the clinical trial or the sham group. The blending process was done by using

The sham procedure to guarantee there will not be biased information [40]. According to this procedure, the electrical stimulation equipment was arranged in the same form and machine, but the machine was not activated in the sham group. This is done in order to guarantee the internal validity.

The clinical group consists of 63 people, while the sham group consists of 77 people. The data of each participant were noted by the staff. When the participants experience a migraine ictal, they were put into their groups in accordance with the lottery. The Subjects didn’t know which group they belong to. A data collecting staff gave instruction to the staff who measures the endogenous exhaled NO level and did the therapy in accordance with the instruction
has given by the staff who understands the group classification (the data collecting staff). The result of the endogenous exhaled NO level before and after the treatment of clinical trial and the sham group was taken care by special staff. Stimulation was done for 30 minutes, and then the measurement and the endogenous exhaled NO level before and after the stimulation is written down, according to with the ATS procedure. All data were known and given to the data collecting staff who works under the main researcher and responsible for carrying out the research.

Both groups (clinical trial and sham) were given 1000 mg paracetamol, in accordance with the migraine pain procedures. Pharmacodynamically, the medicinal therapy shows an effect one hour after the medicine was taken. The research is stopped and an interim analysis is done if the number of the participant in the group is estimated to fulfill one-third of the number of subjects planned. An interim analysis is done in accordance with the O’Brien-Flemming formula concerning the rules of ending clinical test [42-46]. Analysis based on the O’Brien-Flemming criteria was
that when achieving a stopping rule = 0.005, then the research is stopped to fulfill the research ethics. The analysis resulted in a point of 0.005 so there was a significant difference between the clinical groups compared to the sham group. The research was stopped because of the belief that there is a clearly clinically significant effect size based on the previous investigations so that the number of subjects is much smaller than predicted.

There is a significant difference on the sham group+paracetamol comparing to the electrical, clinical test+paracetamol concerning the endogenous exhaled NO level and the pain degree in the VAS scale before and after the electrical stimulation. There is no difference in the age range of two groups.

The result of this research can be applied to the larger population because it fulfills the causal result relation requirements which are mentioned in literature;

1. There is a clear time relation between cause and result [47].

In this research, there was a clear cause-result relation concerning the electrical stimulation effects with the decrease of the pain of the migraine sufferer. There was no difference in the migraine pain pathophysiology between the subject and the migraine cases in the population.
2. There was a strong causal-result relation [47].

The relation between the electrical stimulation to the decrease on the VAS scale, bias is removed by randomization.

3. The relation between response and dose [47].

It is clearly seen that the stimulation frequency influenced the sufferer's response concerning the decrease of pain intensity and the endogenous exhaled NO level. The similar thing is predicted to happen in the population.

4. A specific cause-result relation [47].

The electrical stimulation could clearly decrease the VAS scale and the endogenous exhaled NO level. The similar thing is predicted to happen in the population.

5. A reasonable cause-result relation [47].

The relation between the electrical stimulation with the VAS scale and the endogenous exhaled NO level can be explained based on the previous literature study.

6. In connection with the previous researches [47].

This research is designed based on scientific facts and there is a clear connection with the previous scientific researcher.

7. Experimental proof [47].

This research used experimental method, in this case, a clinical trial was done on the subject and sham group.

8. The result is equivalent to other researchers [47].

The result of this result is equivalent to the one done by Van der Schueren, concerning the endogenous exhaled NO level. It is a new experiment in relation to the usage of the NMES equipment used as an abortive therapy on migraine ictal.

9. It is not mentioned in the literature that a nonparametric study can't be used as a basis to make a generalization to the populations.

This research discovered that the frequency distribution of the endogenous exhaled NO on the migraine sufferer was not normal, which occur in some cases in the population. Pathophysiological there is no difference between the migraine sufferer inside the penitentiary or state prison comparing to the migraine sufferer outside the penitentiary, so there was a basis to generalize the result of this research.

This research is done based on some researchers that were done previously on both human and animal. On the level of human and animal, there is a possibility that the electrical stimulation can influence the pathophysiology of a migraine ictal. Research on rats became an approach that the electrical stimulation can cause the release of the NO from the cerebellum tissue. This is strengthened by examining it using Doppler ultrasonography equipment which shows a picture of the widening of the blood vessel around the cerebellum tissue which had been electrically stimulated. There is a weakness in the animal research study; a matching process with the siblings is not done. Nevertheless, the research data gave important information because all bias can be controlled with the experimental method.

Ishao Hashimoto proved that the electrical stimulation can cause a muscle twitch on the muscular abductor policies brevis which then causes the activation of the climbing fiber, purkinje, and cerebellum parallel based on MEG. This fact became the basis to suggest a new therapy which is practical, affordable and easy to do. There are some facts that show a tendency that the electrical stimulation in the form of muscle twitch can play a role in the pain therapy. Hsneh TC, Cheng PT, Kuan TS and Hong CZ did a research by giving electrical stimulation that causes muscle twitch on the top part of the Trapezius muscle for the myofascial pain therapy. Gaines, J, Metter E dan Talbot L did a clinical trial research in two groups, with the total subjects of 38 people. It didn't know whether a randomization on the group allocation is done in this research. This research uses the McGill Pain Questionnaire measurement on the 15 minutes electrical stimulation with an NMES equipment that put on the quadriceps femoris muscle of the osteoarthritis sufferer. The result was significant and concluded that the NMES can decrease the pain of osteoarthritis sufferer [48]. Yu and colleagues showed that the percutaneous NMES can reduce the pain intensity. 49 Rochester CL showed that the NMES stimulation on the top part of the movement, muscle shows a clinical repair in COPD patients and the increase in the endogenous exhaled NO level [50]. This strengthens the previous theories, that if a stimulation on the tips of the proprioceptive nerve will activate the dorsal spinal-cerebellar pathway.

The NMES equipment can be used as an electrical stimulation that caused a muscle twitch. A muscle twitch was a part of the LTD on the motor learning process [51,52]. On LTD, NO is produced synergically with endocannabinoids [25, 53, 54]. The unbalance enodakanabonoid level is related to a migraine ictal [8, 11, 23]. Until today, NMES has an equipment used in medical rehabilitation field to train disuse atrophy muscles [55, 56]. This was the first research to test an NMES equipment as an application to reduce the pain of the migraine sufferer. The clinical trial using the NMES equipment was important because it tried to prove a new theory concerning migraine pain therapy. The NMES equipment is easy to be found in Indonesia, affordable and easy to operate. Based on the CEA measurement, there was more benefit which can be gotten than the amount of money that the migraine sufferer must spend.

There were several new things that had done by researchers which can be chronologically seen as follows. In 1994, Balon and Nadler examine the electrical stimulation of the muscle that causes the local endogenous NO level to increase [57]. In 1997, Moore SR and colleagues did a research by using NMES to remove an acute pain in the waist [58]. In 1998, Khartonov and colleagues did a research to examine the endogenous exhaled NO level of women's menstruation cycle [58]. In 2002, Delclaux and colleagues did a research on the cirrhosis sufferer; there was a massive increase in the production of endogenous exhaled NO before and after ascites [19]. In 2003, Nathalie Lara and colleagues did a research on the endogenous exhaled NO level and the systematic during a panic
attack induction. Blind test, randomization, and crossover had done in this research [60]. In 2003, Matharu and colleagues did an electrical stimulation that was put on the sub-occipital area of 8 acute migraine sufferers [35]. In 2005, Vints and colleagues did a clinical trial research concerning the relation between a vegetable diet rich in NO (mustard greens, spinach, parsley, and cabbage with the endogenous exhaled NO level [61]. In 2006, Jeffrey A. Dusek and colleagues did a research concerning the relation between oxygen consumption to the production of the endogenous exhaled NO level as a result of the relaxation response in the form of Taichi and meditation. A clinical random blind test is done in this research [62,63]. In 2006, Myers and colleagues proved that the electrical stimulation can reduce depression and facilitate relaxation [64]. In 2007, Roosink and colleagues did a research by using the Percutaneous Neuromuscular Electrical Stimulation (P-NMES) as a therapy for the acute shoulder pain sufferer, showing a clinical repair in the form of the disappearance of the pain [49]. In 2008, Matsumoto examines the increase of the endogenous exhaled NO level of the increase of physical activity, up to 3 times [65]. In 2009, D.C Van der Schuener and colleagues did a research whether during an acute migraine ictal in 2-72 hours, there was an increase in the endogenous exhaled NO level, and based on the increasing activity of iNOS and examining the effectivity of the GW 273629 substance as an iNOS impeding therapy during an acute migraine ictal. The research is done by giving a single dose of GW 273629, a substance that is predicted as the inhibitor of the unspecific iNOS (iNOS and nNOS) that were given during an acute migraine ictal, 1500 mg on 15 migraine sufferers. The endogenous exhaled NO level was monitored with an endogenous exhaled NO analyzer. The result of Van der Schuener and colleagues’ research shows no clinical repair towards an acute migraine ictal during the usage of this substance. And during a migraine ictal, it is known that the production of the endogenous exhaled NO was beyond normal. This research uses equipment with the endogenous exhaled NO analyzer/equipment specification, CLT 88 sp, Eco Medics, made in Switzerland. This equipment is used in accordance with the American Thoracic Society (ATS) guidelines [19]. The research shows the endogenous exhaled NO level is much higher on migraine ictal with the average of 12.5 ppb comparing to interictal 9.9 ppb.17

Conclusion
This research did a stimulation of the median area by using NMES until a muscle twitch occurs, with the same wavelength used by Ishao Hashimoto, 0.2 m/second, for migraine pain therapy, related to the activity of climbing cerebellum fiber with the investigation on the role of the NO and endocannabinoids. A clinical random blind test was done. The endogenous exhaled NO used, Niox Mino, is different than the one used by Van der Schuener, it is more practical but still appropriate with the ATS recommendation [19]. A 10 year CEA measurement had done on a patient who fulfills the inclusion criteria, with the result as follows. If the patient uses the additional therapy, in the form of NMES equipment for 10 years, then it means an additional charge for purchasing the equipment and also medicine to abort a migraine ictal. The price of NMES equipment Rp. 2,500,500, 4 A3 batteries for one equipment @ Rp.4, 000. (The batteries can stay for 30 electrical stimulations, 30 minutes duration for each stimulation). If a sufferer experiences 9 attacks a month, then 9x12x10: 4x4,000 = Rp. 1,080,000. The total cost in 10 years = Rp. 3.580,000, so the additional charge that the patients must pay is Rp. 3,580,000: 10: 12 = Rp. 29,833,33. This additional charge is equivalent to the benefit that the patients could get when experiencing an acute migraine ictal.

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