Research

The Profile of the Level of Endogenous Exhaled NO on the Migraine Sufferers

Arman Yurisaldi Saleh1*, Hasan Machfoed2 and Kuntoro1

1Division of Neurology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia

Abstract

Introduction

Migraine is a health problem which had a big impact. A neurochemistry change in the dura, that is the increase of the amount of nitrite oxide, originated from an excessive NOS (inducible NOS) activation during ictal. Some researchers assume NO as a main cause of the pain intensity in ictal. Migraine diagnosis is guided by the International Headache Society. Hopefully, this examination can be used as a more objective diagnosis in the future.

Methods

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). A Descriptive analytic study to find the level of endogenous exhaled NO on 91 subjects, consisting of 30 normal people, 31 interictal, 30 ictal. Exclusion was done previously. A validation equipment and measurement had been done in accordance with American Thoracic Association guidance.

Results

The level of endogenous exhaled NO in the normal group (median=5), interictal group (median=11), ictal group (median=14). Coefficient correlation between VAS and level endogenous exhaled NO was 0.815.

Conclusion

There is an increase of the NO endogen level in the normal people, migraine interictal, and ictal. Strong correlation between the intensity of pain (VAS) and level endogenous exhaled NO during ictal.

Key Words: A Migraine; Endogenous Exhaled NO

Introduction

A migraine is a health problem occurring in the society which had quite a big impact on the sufferer. Every year, ten million people in the United States are suffering from a migraine. Sixteen percent of the total population suffers from a migraine. This happens mostly to women than men (18%; 16%). In Surabaya, in 1984, amongst the 6,448 new patients at the clinic, 180 people are migraine sufferer [1]. At the Cipto Mangunkusumo Hospital, Jakarta, from the 1,298 new patients that come from January to May 1988, 273 of them are migraine sufferer [2]. A population study in Bogor shows that 61 % of headaches occur in the age group of 25-54, 8.6 % of this group suffered from a migraine, with the detail of 81.6 % is suffering from a migraine without aura, 16.8% migraine with aura, 0.6 % migraine with complication, 1.2 % cluster headache [3].

A migraine, defined as one of a chronic hindrance, which has a big impact, usually unilateral, a headache followed by an aura as a symptom [4]. Migraine sufferer experiences a neurochemistry change in the dura, brain membrane, originated from an excessive NOS (inducible NOS) activation that is the increase of the amount of nitrite oxide. Inducible NOS (iNOS) is an enzyme that is proven to increase during an acute migraine ictal. If inducted, this enzyme stays in the blood for 4 hours, whereas nNOS and eNOS don't [5,6]. Some researchers state that NO is the source of a headache. Another researcher disagreed with this statement. NO becomes the source of a headache is the exogenous NO donor, such as GTN (Glyceryl Trinitrate) which broaden the diameter of a blood vessel in a great way that it stimulates the senses to nerve fiber of the blood vessel wall [7,8]. Nitrite Oxide endogen can cause a headache when the process of the disease resulting too much NO. Some researchers proved that NO endogen plays a role as antinociception. But if too much, NO will have a role in hyperalgesia and allodynia [5,10,15]. The development of migraine therapy will improve the quality of life, reduces pain and the attendance list of the workers.

Until now, the migraine diagnosis has based on the International Headache Society criteria and tends to be subjective. There was not yet an objective parameter, such as laboratory examination, which can be used as a source for migraine diagnosis [4, 5, 10, 14, 15]. There was a tendency that the research is merely measuring the endogenous exhaled NO in relation with an acute migraine ictal [17,20]. The measurement of the NOS level in the blood during an acute migraine ictal is not practical because a laboratory examination can be used as a source for migraine diagnosis [4, 5, 10, 14, 15]. There was a tendency that the research is merely measuring the endogenous exhaled NO in relation with an acute migraine ictal [17,20]. The measurement of the NOS level in the blood during an acute migraine ictal is not practical because a laboratory examination

*Corresponding author: Arman Yurisaldi Saleh, Division of Neurology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia, E-mail: armanyurisaldi@gmail.com

Sub Date: July 28, 2016, Acc Date: August 16, 2016, Pub Date: August 16, 2016.

Citation: Arman Yurisaldi Saleh, Hasan Machfoed and Kuntoro (2016) The Profile of the Level of Endogenous Exhaled NO on the Migraine Sufferers. BAOJ Neuro 2: 016.

Copyright: © 2016 Arman Yurisaldi Saleh, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
using radioactive is needed [21]. Measuring the nitrate level in the blood as an image of the NOS activation is proven to be incorrect because due to its instability, whereas nitrate can be in the form of germ metabolism in the intestine [12].

The measurement of the endogenous exhaled NO level of the migraine sufferer is not painful and easy to do. There are many types of the NO exhalation equipment, and they have also been validated and recommended by ATS [20]. Hopefully, this examination can be used as a more objective migraine diagnosis in the future based on the diagnostic study [10, 14, 17].

The research which shows the endogenous exhaled NO level of the migraine sufferer has not yet been done in Indonesia. Until now, there is only one research which measures the endogenous exhaled NO level on the migraine sufferer using NO exhalation equipment done by Van der Schueren and colleagues, who want to prove that there is an increase of endogenous exhaled NO level during an acute migraine ictal [17]. This research found the mean of the endogenous exhaled NO during a migraine ictal, interictal and on normal conditions. The measurement is done in 2-72 hours after an acute migraine ictal but has not yet found any significant differences [6].

**Methods**

This is a descriptive analysis, research study, to find out the endogenous exhaled NO level in the migraine sufferer in-ictal, inter-ictal and on normal conditions. An analysis, whether there is a correlation between a clinical repair in the VAS scale towards the endogenous exhaled NO level is done in this research. This research is done at the clinic of the Pondok Bambu women and children's 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). A descriptive analytic study to find the level of endogenous exhaled NO on 91 subjects, consisting of 30 normal people, 31 interictal, 30 ictal. Exclusion was done previously. A validation equipment and measurement had been done in accordance with American Thoracic Association guidance. The populations were all migraine patients had come to the clinic at the Cipinang Prison Hospital, Jakarta, Cipinang Prison clinic, The Pondok Bambu State Prison, Salemba, Tangerang, Bekasi and private practice. The sample populations were all patients who were migraine sufferer that fulfill the inclusion.

Criteria and they were migraine patients with aura and without aura, in accordance with the IHS (International Headache Society) criteria, with the age range of 19-55, with the educational background of at least high school, male and female, and willing to participate in the research. On the anamnesis, physical check-up neurologically was in normal. Exclusion is done if a migraine attack occurs >10 times a month or if using a prophylactic, or too much physical activity in the last one hour. There is a history of liver cirrhosis, pneumonia, asthma; bronchitis and/or rhinitis that has been proven by a skin prick test, and saline challenge test. Consuming medication containing NO donor, such as nifedipine, regularly. Following relaxation exercises, such as Yoga, Tai Chi, Qi-gong and the kind. Consuming supplement/medicine which contains arginine and/or nitrate in the last twenty hours, smoking, hypertension, in the ovulation condition, and using hormonal contraception. The research data are written in forms. After going through an editing and coding process, the research data is then recorded on a magnetic disc to undergo a cleaning process. The median of endogenous exhaled NO level of a migraine inter-ictal group and in the normal conditions is done by using a Kruskal-Wallis test. The correlation between VAS and endogenous exhaled NO is tested using a Spearman or Pearson test.

**Results**

According to the table 1, there is a significant difference between three migraine groups. According to the Table 2, there is a strong correlation between VAS with the endogenous exhaled NO level.

| Table 1: The comparison of the endogenous exhaled NO level |
|----------------|-------|--------|
| Migraine ictal | 30    | 14.0   |
| Migraine not in-ictal | 31    | 11.0   |
| Normal         | 30    | 5.0    |

According to the table 1, there is a significant difference between three migraine groups. According to the Table 2, there is a strong correlation between VAS with the endogenous exhaled NO level.
Discussion

The research was held on February 17th, 2010 to July 31st, 2010 after receiving a permit from the Ethical Committee (February 16th, 2010), which was also given by the Director General of the Law and Human Rights Department, to do a research on the inmates as the subject (October 20th, 2009). The research was concentrated in the clinic of the Pondok Bambu women and children’s prison, located in East Jakarta. The subjects of the research were as follows: a migraine ictal group consisting of thirty people, migraine inter-ictal group consisting of thirty-one people, and the normal group consisting of thirty people. The participants consist of 77 women and 14 men. This was suitable for the previous research which proves that the majority of the migraine sufferer were women, because hormonally, the estrogen can influence the endothelial cell of the respiratory tract when releasing the NO to the

Respiratory tract [4] the validity selection in this research can be evaluated according to the valid selection criteria, that was the criteria for migraine diagnosis based on the International Headache Society (IHS). The diagnosis, guidance book can be found on the internet, on free sites which provide research materials. The explanation of the diagnostic criteria can be understood easily by medical staff. According to IHS, the migraine diagnosis criteria were the criteria that are most valid nowadays, so this research has good selection validity.

The research staffs were medical staffs consisting of doctors and clinic paramedic of the state prison that do their duty during the working hours and outside of the working hours (the night shift at the clinic). The research staffs were able to diagnose migraine cases, tension-type headache, and mixed migraine and tension-type headache, after some training was given by the main researcher and some valid IHS guidance book were given. The recruitment of the research subject was done on the place where the research resources were available. The research subjects were analyzed, the diagnosis was done and subjects were given medicine and free consultation by the staffs for twenty-four hours. This research was not easy to be held at medical centers with the intense care unit which only serve patients during working hours only, such as a local government clinic that does not deal with treatment.

This research is done in the Care Unit clinic Pondok Bambu Prison, East Jakarta, most of the research subjects were prisoners of the prison with the capacity of 2000 people, consisting of children (below 19 years old) and women. The number of prisoners may change from time to time, in accordance with their law procedures. This condition cannot be achieved if the research is done in another health clinic.

The level of education of the prisoners varies, from primary school dropouts to university graduates. This research uses the minimum limit education level of high school to make the research procedure easier. The research subjects were also employees of the state prison and correctional facility, who are willing to participate in the research.

The measurement of the endogenous exhaled NO is done by using calibrated Niox Mino equipment. Niox Mino was one of the Aerocrine products (Stockholm, Sweden) which were recommended and validated by the ATS [22]. This equipment also has a good reliability [23]. The measurement method is explained to the subjects in detail, also using a recorded video (downloaded from the free sites on the internet) which shows the usage of the equipment. The room condition during the measurement has the same temperature and humidity by using an air conditioner for twenty-four hours.

The measurement of the endogenous exhaled NO on the migraine sufferer in-ictal is done for not more than thirty minutes after the pain occurred. This is to reassure the relation between the times of the attack with the increase of the NO endogen exhalation. In Van der Schueren and colleagues’ research (the previous research), the time of measurements is not the same. The Measurement has done during the period of 2-72 hours for the pain occurs.

There was a pause during the research when facing a problem concerning the number of the subject which was rather difficult to increase. The difficulty was due to one of the procedures that made the patients uncomfortable, which is the skin prick test. This test is one of the tests that the subject has to undergo, if she/he is willing to participate in the research. Although the number of subjects is not as planned previously, the number of the subject of this research is still greater than the previous one. The problem concerning the number of subjects was the result of the research would have a clinically significant, but not statistically. But in reality, the result of the research has both clinical and statistically significant. This is due to the fact that on the first measurement of the sample, the researcher used effect size 1 and 1.5 based on the judgment of the previous research with the limited literature source (Van der Schueren and colleagues), and using big standard deviation 6. That kind of measurement affected the number of the subject; it became big, 574 for every group. After the research was done and stopped due to the small number of subjects, the result of the clinically and statistically significant was reached, so that with the small number of subjects, the effect size can be detected and statistically significant. This research also shows a significant difference statistically and clinically, concerning the level of endogenous exhaled NO between a migraine during ictal, not in ictal and normal group.

The statistic analysis used a comparison of more than two groups that did not come in pairs; the migraine sufferer in-ictal group, migraine sufferer inter-ictal group, and normal group. The data distribution shows not a normal distribution, shown by skewness curve. Each data does not show any forms of the normal frequency distribution. Statistically, this can become a proof that the similar thing will appear in a larger population. Adding the number of the population will not change the skewness curve form in the normal distribution form (bell shaped) [24]. Only the kurtosis curve form will change into a bell shape if the number of population is increasing [25]. A transformation is done to know if the normal
distribution frequency in another mathematical form will be achieved by using software state. The result of this data processing shows that the distribution frequency is still not normal so that the data processing is in the form of nonparametric. There is a strong correlation between VAS and the endogenous exhaled NO. This supports the hypothesis that NO is the pain mediator during the migraine attack.

This research proves the hypothesis that the endogenous exhaled NO is different from the normal group, migraine inter-ictal group and migraine ictal. Pathophysiologically, this can be explained based on the previous researches. The migraine sufferer experiences a neurochemistry change inside the dural membrane, there is an increase of NO that comes from excessive iNOS (inducible NOS) activation. Inducible NOS is an enzyme that is proven to increase during an acute migraine ictal [10, 17]. When inducted, this enzyme can last inside the blood for 4 hours, whereas eNOS and nNOS don't [4,6]. Some researchers state that NO is the cause of a headache, while other researchers deny this opinion [13].

The NO that causes a headache is the NO exogen donor, such as GTN (Glyceryl Trinitrate) which can widen the diameter of the blood vessel in a vast way, so that a stimulation on the sensory nerve fiber located on the blood vessel wall occurred [7-9, 26]. Endogenous NO can also cause a headache if the process produces too much NO, if the iNOS activation is too much, then the NO produced will also be too much.

This research found new numbers, comparing to the previous one. The average of a migraine ictal is 16.13 ppb, migraine inter-ictal 11.23 ppb, and normal 6.67 ppb with a significant difference. Van der Schueren achieved the average number which shows that the NO exhalation during the migraine attack 12.5 ppb, comparing to the one before the attack is 9.9 ppb, with a significant difference [14]. This difference is probably due to:

1. The NO exhalation analyzer equipment used in this research is different [14].
2. Van der Schueren and colleagues did not explain whether the subject of the research fulfills the IHS criteria as a pure migraine sufferer or mixed (a mixed migraine and tension-type headache). This research did not mention if the subject suffers from a mixed kind of a headache (a mixed migraine and tension-type headache) [14].
3. Van der Schueren and colleagues did not exclude the confusing factor completely before examining the endogenous exhaled NO level.
4. Van der Schueren and colleagues did not mention the time of measurement of the endogenous exhaled NO level clearly, starting from the time when the pain of a migraine first appears. In this research, the measurement was done not more than 30 minutes from the time the patient first felt the pain.

This research is very important because the endogenous exhaled NO was considered to have an important role in a pathophysiology migraine. This is the second research after the one done by Van der Schuener and colleagues. The endogenous exhaled NO level is hoped to be able to become an added criteria to make the migraine diagnosis most objective, compared to the one only based on IHS clinical criteria. The basis of this research is in accordance with Van der Schueren's, and can provide valuable input for researchers in relation to the role of endogenous exhaled NO in the migraine pathophysiology and even researches relating to other diseases.

The endogenous exhaled NO equipment, Niox Mino analyzer, is new equipment in Indonesia. This equipment has a high reliability towards the NO analyzer from the previous generation. Although very modern, the subjects still need to practice it by watching the demonstration on recorded video. If failure during the measurement occurs due to the inability of the subject to use the equipment, so that the research must be done from the beginning again, this resulted in an increase in cost. The application of endogenous exhaled NO level measurement can be done in a clinic in Indonesia, but first of all, equipment socialization must be done.

This kind of research is difficult to be done at health centers, due to the inability to provide such modern equipment, because the price of the equipment is too expensive. But it is hoped that this equipment can be used massively for the benefit of the people. Comparing to the equipment used in Van der Schueren's research, the Niox Mino has advantages in its small size and light weight. [17,22]. This equipment can produce endogenous exhaled NO automatically so that it can achieve high validity and reliability [21]. This equipment can also be accepted socially, culturally and religiously.

References

1. Machfoed H (2005) Perubahan tingkat intensitas nyeri kepala, stres psikologis, depresi, kecemasan dan kadar nitrit serum, pada penderita nyeri kepala tipe tegang kronik, penelitian pengukuran parameter sensitivitas sentral dari trigeminal nukleus kaudalis [Dissertation]. Surabaya: Airlangga.
2. Riyanto B (1995) The Head Pain Diagnosis Problem. Cermin Dunia Kedokteran 104.
3. Misbach J (2006) Epidemiologi of headache in Indonesia. PERDOSSI Bogor.
4. Olesen J, Lance JW (2004) Chepalalgia The international classification of headache disorders second edition 24(1).
5. Villalon CM, Centurion D, Valdivia L, De Vries P, Pramod RS, et al. (2003) Migraine: pathophysiology, pharmacology, treatment and future trends. Curr Vasc Pharmacol 1(1): 71-84.
6. Gupta S, Mehratra S, Villalon CM, Perusquia M, Pramod RS, et al. (2007) Potential role of female sex hormones in the pathophysiology of a migraine. Pharmacology & Therapeutics 113(24): 321-340.
7. Evans GJO (2007) Synaptic signaling in cerebellar plasticity. Biol Cell 99(7): 363-378.
8. Pacher P, Batkai S, Kunos G (2006) The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 58(3): 389-462.
9. Evers S (2004) Botulinum toxin and the management of chronic headaches. Curr Opin Otolaryngol Head Neck Surg 12(3): 197-203.
10. Arulmani U (2004) Calcitonin Gene-Related Peptide and Migraine: Implications for Therapy. India: Madras.
11. Durham PL, Russo AF (2003) Stimulation of the calcitonin gene-related peptide enhancer by mitogen-activated protein kinases and repression by an antimigraine drug in trigeminal ganglia neurons. Neuroscience 23(3): 807-815.
12. Greco R, Gasperi V, Maccarrone M, Tassorelli C (2010) The endocannabinoid system and migraine. Exper Neurol 224(1): 85-91.
13. Goadsby P, Lipton F, Ferari L (2002) Migraine-current understanding and treatment. NEJM 346(4): 257-270.
14. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, et al. (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 8(2): 136-142.
15. Reuter Uwe, Bolay Hayrunnisa, Jansen-Olesen Inger, Chiarugi Alberto, et al. (2001) Delayed inflammation in rat meninges: implications for migraine pathophysiology. Brain 124(12): 2490-2502.
16. Sokolovic E (2005) Prevalence of a tension-type headache and migraine among the employees of the Swiss University hospital, their impact on disability, headache management and economic impact for the employer. [Thesis] 1-5.
17. Schuere B, Lunnon MW, Laurijssens BE (2009) Does the unfavorable pharmacokinetic and pharmacodynamic profile of the iNOS inhibitor GW273629 lead to inefficacy in an acute migraine. J Clin Pharmacol 49(3): 281-290.
18. Baysal A (2001) NO I: advances in the measurements for clinical applications. Turk J Med Sci. 31(6): 471-476.
19. Malmstrom R, Tornberg D, Settergren G (2003) Endogenous NO release by vasoactive drugs monitored in exhaled air. Am J Respir Crit Care Med 168(1): 114-120.
20. Wang C LC, Lin H, Yu C, Chung K, H K, et al. (1998) Increased exhaled NO in active pulmonary tuberculosis due to inducible NO synthase upregulation in the alveolar macrophage. Eur Respir J 11(4): 809-815.
21. Moshage H (1997) Nitric oxide determination: much ado about NO thing? Clin Chem 43(4): 533-556.
22. (2005) American Thoracic Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory NO and nasal NO, 2005. Am J Respir Crit Care Med 171(8): 912-930.
23. Alving K, Janson C, Nordvall L (2006) Performance of a new handheld device for exhaled NO measurement in adults and children. Respiratory Research 7(67).
24. Sanders (1990) Statistics a fresh approach.
25. Kurihara N, Alfie M, Sigmon D (1998) Role of nNOS in blood pressure regulation in eNOS null mutant mice. Hypertension 32(5): 856-861.
26. Matharu M, Weiner R, Goadsby PJ (2004) Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 127(1): 220-230.