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Vasomotor reactivity measurement using Breath Holding Index to objectively diagnose migraine in Indonesia

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ABSTRACT

Objective. Migraine is currently diagnosed using the subjective fulfilment of the International Headache Society (IHS) criteria. Considering the pathophysiology of endothelial dysfunction in migraine, this study aimed to utilize the breath holding index (BHI) to diagnose migraine objectively by assessing the vasodilatation response of intracranial arteries in migraine without aura.

Material and method. 128 subjects with primary headache in the interictal phase were cross-sectional recruited and classified into migraine and non-migraine groups. BHI was performed using transcranial Doppler examination. Confirmed migraine was diagnosed using the validated IHS-equivalent Indonesian Migraine Screen Questionnaire (MS-Q) score of ≥4, BHI of <0.69, and one-month clinical response to topiramate and/or indomethacin administration based on the nature of their headache.

Result. This study enrolled 104 and 24 subjects with migraine and non-migraine headache, respectively. The sociodemographic profile was similar between groups. Reduced ipsilateral BHI was more observed in the migraine than the non-migraine group (0.70 vs 1.53, p<0.001), with sensitivity of 49 (39-59) % and specificity of 92 (81-100) % using the established cut off value of 0.69.

Conclusion. The breath holding index is a highly specific, moderately sensitive and objective tool to diagnose migraine. Measurement of vasoconstrictive response may be considered to further increase the sensitivity of this objective diagnostic tool.

Keywords: breath holding index, migraine, migraine vascular index, transcranial Doppler, vasomotor reactivity

INTRODUCTION

Headache is a subjective sensory and emotional symptom of discomfort due to the activation of pain-sensitive structures in the head or neck. This symptom may be secondary due to actual or potential damage in the head or neck structure, or primary without underlying diseases (including migraine) [1]. Headache is one of the most commonly reported complaints [2], reaching 90% according to the Indonesian Neurologists Headache Study Group [3], and contributes as the seventh cause of disability according to The World Health Organization (WHO) [4].

To date, migraine is diagnosed by matching the subjective headache characteristics reported by the patients to the diagnostic criteria established by the International Headache classification [1]. The Indonesia Migraine Screen Questionnaire (MS-Q) was developed to aid the process [5]. Nevertheless, sub-

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jective complaints may have several limitations, including the differences in understanding and perceiving headache between subjects and clinicians. Many other secondary headaches, including cervicogenic headache, occipital neuralgia, and sinus headache, may also resemble migraine [6]. Misdiagnosis was reported in at least 50% cases [7], which resulted in delayed and inappropriate management, increased disability, and reduced the quality of life of the subjects [8,9]. As this disease predominantly occurs in young adulthood, migraine also has a substantial impact on work productivity. An objective measure is needed to overcome this issue.

Endothelial dysfunction has been proposed as a risk factor in an estimated 60% of migraine cases. Endothelial dysfunction may interfere with vasomotor reactivity, disrupt the maintenance of normal cerebral blood flow (CBF) due to fluctuations in systemic hemodynamic and blood carbon dioxide (CO_2), and induce inflammation of intracranial and extracranial vessels [10]. All conditions may precipitate cortical spreading depression, which has been proposed as the pathophysiology of migraine [11]. The association between reduced vasomotor reactivity and migraine has been reported in some studies, including Kastrup et al., Sedighi et al., and Akgun et al. These studies discovered that subjects with migraine had reduced cerebral vasomotor reactivity response to CO_2, and increased CO2 may induce migraine [12-14]. Therefore, inducing hypercapnia and measuring the vasomotor reactivity and CBF may be a potential parameter to diagnose migraine objectively. Hypercapnia may be simulated using breath holding, thus impaired vasomotor reactivity and reduced CBF can be easily detected using transcranial Doppler by the Breath Holding Index (BHI) [15]. Transcranial Doppler is an ultrasound technique to assess the CBF of intracranial vessels which can be easily be accessed and operated by trained operators.

To ensure the clinical diagnosis of migraine, in addition to the gold standard clinical criteria from IHS, this study also assessed the clinical response after one-month therapy with topiramate and/or indomethacin. Topiramate of 25mg twice daily has been recommended as prophylaxis for migraine, whereas indomethacin is a non-steroid anti-inflammatory drug (NSAID) used to abort other primary headaches [16]. This study aimed to validate BHI as an objective measure to diagnose migraine in Indonesia.

MATERIALS AND METHODS

Subjects

A cross-sectional study was conducted in the neurology outpatient clinic of "Dr. Cipto Mangunkusumo" National General Hospital, Jakarta, Indonesia, from December 2016 to April 2017. The inclusion criteria included adults of ≥18 years old diagnosed with primary headache, not having a headache attack during enrolment, and with a minimal education level of high school graduate. The exclusion criteria included being diagnosed with secondary headache, other neurological abnormalities including post-stroke, stenosis of intracranial blood vessel, cancer, anemia or bleeding diathesis, hypertension, diabetes, thyroid disease, pulmonary disease, psychiatric disorder, being pregnant, consuming antipsychotic, antidepressant, or anti-seizure medication within three months, NSAID within 24 hours, caffeine of ≥500 mg daily, or antithrombotic drugs at the time of examination, as well as having a history of smoking. Screening was conducted clinically and informed consent was first obtained prior to participation in this study.

Measurement of vasomotor reactivity using transcranial Doppler (TCD) and the breath holding maneuver

Vasomotor reactivity was measured using transcranial Doppler with the breath holding maneuver. Both middle cerebral arteries were examined using a 2–MHz TCD machine Digi-Lite (by RIMED LTD., Raanana, Israel) in a resting state (basal state) and a breath holding state. The breath holding index (BHI) was measured after 30 seconds of breath holding. The ipsilateral MCA was the predominant frequent or more intense side of headache. This examination was performed by two neurosonologists, which were blinded to the subject's migraine status and to each other. The normal value for BHI is ≥0.69 [17].

Confirmed migraine diagnosis

The diagnosis of migraine was confirmed using a combination of three measures, which were: the Indonesian version of the Migraine Screen Questionnaire (MS-Q) score of ≥4, positive BHI of <0.69, and clinical response following topiramate. The MS-Q was a validated questionnaire based on the diagnostic criteria from IHS. The positive BHI was obtained using the results of TCD.

Following the MS-Q Indonesia and TCD-breath holding procedure, every patients would receive topiramate 2x25mg daily for a month or indomethacin 200mg every attack. Topiramate was prescribed to those with MS-Q ≥4 or positive BHI test whereas the rest would receive indomethacin. All subjects were obliged to document their headache pattern using a headache diary.

Confirmed migraine was determined for those receiving topiramate if there was a ≥50% decrease in headache frequency or duration, a ≥40% decrease in headache intensity, or a ≥40% average decrease in those aspects. Confirmed non-migraine was determined if these criteria were not fulfilled. Confirmed

non-migraine was also diagnosed if subjects receiving indomethacin had the headache aborted for a month. However, those with persistent headache after indomethacin would receive topiramate 2x25mg daily for an additional month to determine the confirmed migraine status.

Statistical analysis

Statistical analysis was conducted using SPSS version 20.0. Data were provided in percentages for categorical data, mean ± standard deviation for normally-distributed numerical data, or medians (minimum-maximum) for abnormally-distributed numerical data. The sensitivity, specificity, and the area under the curve (AUC) of BHI were calculated using the cut-off from previous research of 0.69 [17,18].

Ethical clearance

This study protocol was evaluated and approved by the Research Ethics Committee Faculty of Medicine Universitas Indonesia No. 998/UN2.F1/ETIK/2016 as well as "Dr.Cipto Mangunkusumo" Hospital No. LB.02.01/X.2/180/2017.

RESULTS

Study profile

There were 168 subjects with headaches during the study timeline, of which 30 subjects were excluded and 10 subjects dropped out. The reasons for exclusion included the final diagnosis of secondary headache (25 subjects), some were diagnosed with other neurological conditions (3 subjects), they were on warfarin (1 subject), or they refused to follow the breath holding protocol (1 subject). The reasons for dropping out included refusal to consume the migraine confirmatory medication (2 subjects), non-compliance with medication consumption (4 subjects), distance and transportation issues in relation a follow-up visit (3 subjects), and pregnancy (1 subject). In the end, 128 subjects were recruited to this study.

Confirmed migraine and non-migraine diagnosis

Confirmed migraine was diagnosed using a combination of MS-Q, BHI, and clinical response after migraine medication. Using MS-Q ≥4 and BHI ≥0.69, there were 32 subjects who were MS-Q and BHI positive, 32 subjects who were MS-Q positive and BHI negative, 32 subjects who were MS-Q negative and BHI positive, and 32 subjects who were both MS-Q and BHI negative. Therefore, there were 96 confirmed migraines and 32 confirmed non-migraines using MS-Q and BHI in the first phase.

The second phase, regarding clinical response to topiramate or indomethacin was performed on each subgroup containing 96 confirmed and 32 non-confirmed migraine subjects, respectively. From the first subgroups, there were 2 subjects who were not responsive to topiramate (1 subject had MS-Q and BHI positive, 1 subject had MSQ negative and BHI positive). Therefore, there were 94 confirmed migraine and 2 confirmed non-migraine diagnosis at the second phase.

On the other hand, out of 32 subject in the second subgroup, there were 11 subjects who were unresponsive to indomethacin, and they received topiramate for an additional month, and in 10 of 11 subjects the headache was resolved. Therefore, there were 10 additional confirmed migraine and 22 additional confirmed non-migraine diagnoses in the second phase.

In conclusion, this study recruited 104 subjects with a diagnosis of confirmed migraine and 24 subjects with confirmed non-migraine.

Baseline characteristics

This study recruited mostly female subjects (80.77% vs 87.50% in migraine vs non-migraine, p=0.36) with an average age of 33.4±8.5 vs 31.6 ± 9.9 years in migraine vs. non-migraine subjects (p=0.56), respectively. A similar sociodemographic profile was also observed in terms of level of education, profession, family history of migraine, and the predominant side of headache in both groups (Table 1).

TABLE 1. Subject characteristics (n = 128)

Parameters	Confirmed migraine (n = 104)	Confirmed non-migraine (n = 24)	*p*
Age (years)	33.4 ± 8.5	31.6 ± 9.9	0.36[a]
Female, n(%)	84 (80.8)	21 (87.5)	0.56[b]
Education level, n(%)			0.28[c]
High school	16 (15.4)	8 (33.3)	
Diploma	30 (28.9)	8 (33.3)	
Undergraduate	49 (47.1)	8 (33.3)	
Postgraduate	9 (8.6)	0 (0)	
Profession, n(%)			
Medical	36 (34.6)	4 (16.7)	0.56[c]
Non-medical	59 (56.7)	17 (70.8)	
Not working	9 (8.7)	3 (12.5)	
Family history, n(%)			
Yes	42 (40.4)	4 (16.7)	0.63[c]
No	43 (41.4)	14 (58.3)	
Unknown	19 (18.2)	6 (25.0)	
Dominant side, n(%)			
Right	64 (61.5)	14 (58.3)	
Left	40 (38.5)	10 (41.7)	0.77[d]

a - Mann-Whitney test, b - Fisher test, c - Kolmogorov-Smirnov test, d - Chi-square test

Flow dynamics of MCA using transcranial Doppler and the breath holding maneuver

This study observed reduced peak systolic velocity (PSV), end diastolic velocity (EDV), and mean flow velocity (MFV) in ipsilateral MCA in the subjects with confirmed migraine compared to the non-migraine subjects. This remained consistent after the breath holding maneuver, with PSV of 111.49 vs. 134.53 mmHg (p=0.001), EDV of 51.81 vs. 64.80 mmHg (p=0.004), and EDV 71.71 vs. 88.02 mmHg (p=0.001) in confirmed migraine vs. non-migraine subjects, respectively. The BHI was also significantly lower in confirmed migraine (0.70 [0.03-2.59]) than non-migraine (1.53 [0.34-4.39]) subjects (p<0.001).

In the view of the contralateral MCA measurement, there were also reduced PSV (118.60±27.86 vs. 131.89±27.30, p=0.040), EDV (57.78±18.01 vs. 65.53± 18.36, p=0.065), and MFV (77.98±20.75 versus 87.63 ± 20.54, p=0.045) in migraine vs. non-migraine subjects, respectively. This phenomenon was also observed after the breath holding maneuver, with PSV of 67.85 ± 17.75 vs. 78.51±21.76 mmHg (p=0.014), EDV of 16.20 ± 8.93 vs. 25.37±10.86 mmHg (p=0.001), and MFV of 33.42±10.75 vs. 42.20±13.23 mmHg (p=0.001) in confirmed migraine vs. non-migraine subjects, respectively. However, the BHI was not statistically different between groups (1.14 [0.00-3.70] vs. 1.56 [0.23-5.08] in migraine vs. non-migraine, respectively, p=0.07).

TABLE 2. Diagnostic performance of BHI for migraine (n=128)

	Cut-off Value	Migraine diagnosis		Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC, %
		M	NM			
BHI.i						
+		51	2	49 (39-59)	92 (81-100)	70.4
-	0.69	53	22			
BHI.c						
+		26	2	25 (17-34)	91 (80-100)	58.3
-		77	21			

AUC, area under the curve; MVI, migraine vascular index; BHI, breath holding index; c, contralateral; i, ipsilateral; NM, confirmed non-migraine; M, confirmed migraine

DISCUSSION

Determination of confirmed migraine and non-migraine diagnosis

Diagnosing migraine may be challenging due to its subjective nature, with no established objective measures to date. The gold standard diagnostic criteria of migraine using the IHS criteria in this study led to the diagnosis of 96 migraine and 32 non-migraine subjects. However, combining that criteria with BHI and clinical response to medication, this study detected an additional 8 subjects with confirmed migraine. The additional effort to ensure the confirmed migraine diagnosis was one of the strengths of this study. This finding also underlined the importance of other measures to improve the diagnosis of migraine, especially using objective means.

The characteristics of the study subjects

This study enrolled mostly female subjects in their thirties. Young female adults tend to have migraines due to the predominant X-linked inheritance [19], as well as the positive association of female reproductive hormones and migraines [20]. Rajan et al. also described a 4:1 ratio of females to males with migraines [21]. The lack of a difference between the migraine and non-migraine groups in respect to age and gender may eliminate the influence of those two confounding factors in the analysis.

Education was another important confounding factor in this study due to its inverse relationship with migraines, as described by the National Health Interview Survey (NHIS) in 2011 and Han et al. [22]. This fact led to the exclusion criteria of lower education background. The similar level of education between the migraine and non-migraine groups may also eliminate the influence of education in the analysis.

The predominance of headaches on one side is one of the migraine diagnosis criteria. However, some studies have described that only about 15% subjects with migraines experienced the pure-lateralization characteristics of migraine, and almost half of the migraines were bilateral [23,24]. This study described 61.5% and 58.3% subjects with right-sided vs. left-sided headaches, respectively. The difference was not statistically significant (p = 0.77).

Vasodilation response to the breath-holding maneuvre

Cerebral vessels have an endothelium and have the ability to autoregulate themselves in response to systemic change, including CO_2 or blood pressure, to maintain constant CBF. Increased CO_2 stimulates cerebral vasodilatation and increased CBF [25], which is mediated by the increased vasodilatory mediators of prostacyclin (prostaglandin I2), endothelium-derived relaxing factor, or nitric oxide (EDRF/NO), S-nitrosothiols (RSNOs), and endothelium-derived hyperpolarizing factor (EDHF), as well as the decreased vasoconstrictive mediators of endothelin-1, peroxynitrite (OONO-), and endothelium-derived constricting factors (EDCF) [26,27].

Lower PSV, EDV, MFV, and BHI levels in migraine subjects may be associated with the pathogenesis of endothelial dysfunction in migraines. Endothelial dysfunction may decrease smooth muscle tone, reduce production of vasodilatory mediators, increase peripheral resistance, and impair vasomotor reactiv-

ity [28]. Some studies have supported the impaired vasomotor reactivity in migraines. After the breath -holding maneuvre, Akgun et al. described a lower MFV of 58.17±14.14 vs. 61.05±11.74 in migraine vs. non-migraine subjects, respectively (p=0.229). In addition, the vasodilation response following hypercapnia was lower in chronic common migraine during the interictal phase [17]. Gonzalez-Quintanilla et al. also reported that PSV and MFV were lower in migraines [29].

This study also supported these studies. The BHI, using the cut-off value of 0.69, provided moderate sensitivity of 49% and high sensitivity of 92% in the ipsilateral MCA measurement. This value was observed to be lower in the contralateral MCA measurement, which provided lower sensitivity of 25%, but with consistent high specificity of 91%. Therefore, a positive finding of BHI <0.69 may objectively confirm the diagnosis of migraine.

While this study had strengths in the careful determination of a confirmed migraine diagnosis, it had some limitations, including the relatively small sample size and the fact that there were potentially more severe migraine sufferers in our tertiary hospital. Besides increasing the sample size and population, other techniques to assess vasomotor response, including the vasoconstriction response, may be considered in future studies.

CONCLUSION

This study supported the evidence that disturbance in vasodilatation, using transcranial Doppler during the breath holding manoeuvre, may be considered as an objective measures for diagnosing migraine. The established BHI cut-off value of 0.69 produced high specificity (92%) and moderate sensitivity (49%), especially when measured ipsilaterally. Measurement of vasoconstriction response may be considered as an attempt to increase the sensitivity of objective diagnosis of migraines in future studies.

What is already known on this topic: Many other secondary headaches, including cervicogenic headache, occipital neuralgia, and sinus headache, may also resemble migraines. Misdiagnosis was reported in at least 50% cases, which resulted in delayed and inappropriate management, increased disability, and a reduced quality of life for the subjects.

What this study adds: This study supports the evidence that disturbance in vasodilatation using transcranial Doppler during the breath holding manoeuvre may be considered as an objective measure for diagnosis of migraines. Measurement of vasoconstriction response may be considered as an attempt to increase the sensitivity of objective diagnosis of migraines in future studies.

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Conflicts of interests:
We declare that we have no conflict of interest

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