European Review for Medical and Pharmacological Sciences 2022; 26: 1939-1944

Diagnostic value of cerebral vasospasm by transcranial doppler ultrasound in Vietnamese patients with subarachnoid hemorrhage

H.-K. VO[1,2,3], V.-T. LE[1,2], V.-L. NGUYEN[1,2], X.-C. DAO[4,5], D.-H. DUONG[6], T.-L. TRINH[1,2], V.-T. NGUYEN[1], H.-L. VO[7], C.-H. NGUYEN[1], V.-L. TRAN[8,2], A.-T. NGUYEN[9], V.-T. HOANG[10], T.-A. TRUONG[11], T.-B. NGUYEN[2], B.-C. CHU[1], T.-M. LE[1], T.-T.-H. DAO[1], T.-H. DUONG[1], H.-Q. HA[1], T.-P.-L. TRINH[1], T.-T. TRUONG[1], V.-D. PHAN[1], T.-N.-L. PHAM[1], T.-H. PHUONG[1], Q.-C. LE[2,12]

[1]Neurology Center, Bach Mai Hospital, Hanoi, Vietnam
[2]Department of Neurology, Hanoi Medical University, Hanoi, Vietnam
[3]Department of Neurology, University of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam
[4]Department of Emergency and Critical Care Medicine, Hanoi Medical University, Hanoi, Vietnam
[5]Department of Intensive Care, Bach Mai Hospital, Hanoi, Vietnam
[6]Vietnam National Heart Institute, Bach Mai Hospital, Hanoi, Vietnam
[7]Institute for Preventive Medicine and Public Health, Hanoi Medical University, Hanoi, Vietnam
[8]National Geriatric Hospital, Hanoi, Vietnam
[9]Department of Neurology and Neuro Intensive Care, Viet Duc University Hospital, Hanoi, Vietnam
[10]Department of Neurology, 108 Military Central Hospital, Hanoi, Vietnam
[11]Nam Dinh University of Nursing, Nam Dinh, Vietnam
[12]Ministry of Health, Hanoi, Vietnam

Abstract. – OBJECTIVE: Although the application of transcranial Doppler (TCD) ultrasonography in clinical diagnosis of cerebral vasospasm is popular in clinical practice in Vietnam, available evidence of the predictive value of vasospasm on TCD in the literature was mostly reported from large institutions in developed countries. Hence, this study was conducted to evaluate the value of TCD ultrasonography in the diagnosis of vasospasm in patients with subarachnoid hemorrhage (SAH) in Vietnam.

PATIENTS AND METHODS: This is a prospective observational study of all aneurysmal SAH patients consecutively admitted to a single center between 2008 and December 2011. TCD and 64-slice computed tomographic angiography (CTA) were used to cerebral vasospasm in SAH patients.

RESULTS: 316 patients were analyzed (mean age = 52.97±12.27 years, 52.2% males). There were statistically significant difference rates of the cerebral vasospasm by Hunt and Hess Classification and Fisher classification (p <0.01). The proportion of the patients with cerebral vasospasm who were diagnosed exactly by TCD was 95.2%, while the proportion of the patients without cerebral vasospasm diagnosed exactly was 91.5%. TCD predictive diagnostic value was the highest, with the sensitivity of 0.95 (95% CI: 0.91-0.98), specificity of 0.91 (95% CI: 0.85-0.96), positive predictive value of 0.94 (5% CI: 0.90-0.97) and negative predictive value of 0.93 (95 CI: 0.87-0.97). Hemiplegia was the clinical symptom with the highest diagnostic value with the sensitivity of 0.34 (95% CI: 0.27-0.41), specificity of 0.92 (95% CI: 0.86-0.96), positive predictive value of 0.86 (95% CI: 0.76-0.93) and negative predictive value of 0.49 (95% CI: 0.41-0.54).

CONCLUSIONS: Evidence of vasospasm diagnosis on TCD ultrasonography was found with high accuracy. Current study enables to suggest the wide application of TCD in Vietnam health facilities from central to grassroots levels instead of the CTA use.

Key Words:
Subarachnoid hemorrhage, Transcranial doppler, Cerebral vasospasm.

Corresponding Authors: Hong-Khoi Vo, MD, Ph.D; e-mail: drvohongkhoi@yahoo.com.vn
Hoang-Long Vo, MD; e-mail: vohoanglonghmu@gmail.com

Introduction

Cerebral vasospasm that occurs after subarachnoid hemorrhage (SAH) caused by aneurysm rupture is one of the leading causes of disability and death[1,2]. Poor treatment outcome of cerebral vasospasm imposes economic costs and consequences of illness for the individual, and families and nations. Approximately 70% of patients between days 3 and 14 following SAH, are reported with angiographic vasospasm, and 20% to 40% of patients develop neurological deficits or infarction caused by delayed cerebral ischemia (DCI)[3-6]. Clinically, the complication of cerebral vasospasm is DCI defined as the development of new focal neurological signs and/or deterioration in level of consciousness, lasting for more than 1 h in patients with SAH[7].

Early diagnosis of cerebral vasospasm is posed when there are no clinical signs in order to propose a timely intervention plan for preventing DCI complications in SAH patients, thereby reducing disability and mortality rates. Transcranial Doppler (TCD) ultrasonography is noninvasive, inexpensive, and easily performed at the bedside, making it particularly appropriate for daily evaluations, obtaining information regarding the collateral flow across various branches of the circle of Willis in patients with cerebrovascular disorders. The measured flow velocity data can assist in the early diagnosis and monitoring of the progression of cerebral vasospasm after SAH, especially SAH due to ruptured cerebral aneurysm. The sensitivity of TCD is the highest for the vasospasm in the proximal middle cerebral artery but decreases in other vascular territories. It also varies depending on the adequacy of vessel insonation. The diagnostic value of TCD comes from its high specificity – detection of normal flow velocities can effectively exclude the presence of vasospasm. It is thus an excellent modality for the initial patient triage[8].

Regarding a developing country as Vietnam, TCD application in clinical diagnosis of cerebral vasospasm is becoming more and more popular in Vietnam instead of routine cerebral CT angiography, which is extremely expensive and contaminated with radiation; however, there have been no studies evaluating the value of TCD in diagnosing cerebral vasospasm after SAH. Hence, we aimed to evaluate the value of TCD in the diagnosis of cerebral vasospasm in Vietnamese patients with SAH.

Patients and Methods

Study Design and Patient

A prospective cross-sectional study was conducted at Bach Mai Hospital from 2008 to 2011. Patients were eligible for the inclusion of the inpatients who (i) were during treatment in our institution (Emergency and Intensive Care Unit, Neurology Center, Bach Mai Hospital, Hanoi, Vietnam) with a final diagnosis of SAH through clinical characteristics and DSA or CT, CTA, (ii) were hospitalized within 24 hours of the onset of a SAH and (iii) were monitored in hospital until at least 21 days. Exclusion criteria included SAH patients who experienced a prior head injury, received previous brain aneurysm intervention, had comorbidities, such as severe coagulopathy, anemia (Hemoglobin < 80 g/L), heart valve disease, HIV, and brain tumor, and failed to detect flow velocity through over the transtemporal window on TCD. A total of 316 patients were recruited to participate in the study.

We evaluated clinical symptoms with corresponding classifications, including hemiplegia, coma, confusion, somnolence, agitation, headache, convulsions, fever, vomiting, nausea, location of aneurysm, Hunt & Hess Classification, and Fisher grading scale. In addition, potential risk characteristics were documented to be gender, age, smoking, alcohol abuse, history of hypertension and diabetes.

All patients gave informed consent to enter the study. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Military Medical University.

Diagnostic Imaging Techniques

TCD ultrasound: all patients underwent TCD ultrasound using the TCD machine (TC 4040, EME/Nicolet, Kleinostheim, Germany). Vasoconstriction was detected using a 2 MHz multi-frequency, transaxial transcranial and meningeal window transducer measuring the mean flow velocity (MCV) in cm per second (cm/s). Vasospasm was diagnosed when MFVs in the middle, anterior, and posterior cerebral arteries through the transtemporal window above 120, 90, and 60 cm/s respectively on TCD, or MFV in middle cerebral artery > 50 cm/s within 24 hours for 2 consecutive days with the presence of a new neurologic abnormality, or the Lindegaard ratio (LR) – ratio of middle cerebral artery to extracranial internal carotid artery (ICA) > 3[9,10].

Computed tomography angiography of the brain: all patients underwent cerebral angiography within 24 hours of admission to find the cause of SAH and diagnose cerebral vasospasm with use of using a 64-slice computed tomographic angiography (CTA; Siemens Medical Solutions, Forchheim, Germany). CTA data analysis was performed between days 3 and 14 after SAH to assess cerebral vasospasm. Vasospasm is defined as a reduction of vessel diameter at the narrowest site ≥ 30% compared to the diameter of the immediately preceding proximal segment of the vessel[11].

The study patients also underwent CTA again whenever TCD showed signs of vasospasm or was clinically abnormal. Herein the study population was divided into two groups: 187 patients with cerebral vasospasm in CTA (group I), 129 patients without cerebral vasospasm on CTA (group II). In the times of TCD ultrasound, patients with vasospasm were immediately transferred to a CTA to confirm the diagnosis.

Statistical Analysis

Data were sorted, cleaned, coded and entered into Epidata 3.1. Then, a software program (Stata® 15; StataCorp LLC, College Station, TX, USA) was used for all statistical analyses. The Chi-squared or Fisher's exact test was used for categorical variables. Value of TCD and clinical symptoms in the diagnosis of cerebral vasospasm were presented with sensitivities, specificities, and positive and negative predictive value. Diagnostic results were expressed as percentage with 95% confidence interval (CI). The level of significance was set at p-value <0.05 in all analyses.

Table I. General characteristics of the study patients.

	Patient (%)
Gender – %	
Male	165 (52.2%)
Female	151 (47.8%)
Age-Mean ± SD	52.97 ± 12.27
Potential risk factor	
Smoking – %	111 (35.1%)
Alcohol abuse – %	113 (35.8%)
Hypertension – %	100 (31.6%)
Diabetes – %	4 (1.3%)
Location of aneurysm – %	
Anterior circulation aneurysm	167 (71.4%)
Posterior circulation aneurysm	71 (28.6%)
Vasospasm * – %	
Yes	187 (59.2%)
No	129 (50.8%)

*Based on the results of 64-slice CTA; SD: standard deviation.

Results

Among 500 patients with SAH treated at our institution, 316 those with SAH met the inclusion criteria for the study. Half of them were men (52.2%). The mean age was 52.97 (SD: 12.27). Potential risk factor included alcohol abuse in 35.8% of the patients, smoking in 35.1%, hypertension in 31.6%, and diabetes in 1.3%. SAH was commonly caused by ruptured brain aneurysms, in which, most of them had anterior circulation aneurysms (71.4%). Depending on the CTA, we documented 59.2% of the patients with cerebral vasospasm after SAH (Table I).

As shown in Table II, there were statistically significant difference rates of the cerebral vasospasm by Hunt & Hess Classification and Fisher classification (p <0.01). Cerebral vasospasms were the most common in patients with grades IV to V (Hunt & Hess Classification), corre-

Table II. Level of clinical symptoms and lesions on CTA by cerebral vasospasm.

	Cerebral vasospasm	Non-cerebral vasospasm	p-value
Hunt & Hess Classification			< 0.01
Grade I	4 (11.1%)	32 (88.9%)	
Grade II	128 (60.7%)	83 (39.3%)	
Grade III	23 (63.9%)	13 (36.1%)	
Grade IV	28 (96.6%)	1 (3.4%)	
Grade V	4 (100%)	0 (0.0%)	
Fisher classification			< 0.01
Grade I	13 (46.4%)	15 (53.6%)	
Grade II	12 (38.7%)	19 (61.3%)	
Grade III	27 (54.0%)	23 (46.0%)	
Grade IV	135 (65.2%)	72 (39.9%)	

Table III. Comparison of cerebral vasospasm between TCD and CTA.

TCD	64-slice CTA		*p*-value
	Cerebral vasospasm	Non-cerebral vasospasm	
Cerebral vasospasm	178 (95.2%)	11 (8.5%)	< 0.01
Non-cerebral vasospasm	9 (4.8%)	118 (91.5%)	

sponding to 100% and 96.6% of the patients. The proportion of cerebral vasospasm was the highest in patients classified as grade IV (Fisher classification) (65.2%), while this figure was the lowest in those with grade II (Fisher classification) (38.7%).

As shown in Table III, the proportion of the patients with cerebral vasospasm who were diagnosed exactly by TCD was 95.2%, while the proportion of the patients without cerebral vasospasm diagnosed exactly was 91.5%. This difference was observed to be statistically significant.

The 64-slice CTA was used as a standard for diagnosing vasospasm in this study. TCD predictive diagnostic value was the highest, with the sensitivity of 0.95 (95% CI: 0.91-0.98), specificity of 0.91 (95% CI: 0.85-0.96), positive predictive value of 0.94 (5% CI: 0.90-0.97) and negative predictive value of 0.93 (95 CI: 0.87-0.97). Regarding the clinical symptoms, hemiplegia was the clinical symptom with the highest diagnostic value with the sensitivity of 0.34 (95% CI: 0.27-0.41), specificity of 0.92 (95% CI: 0.86-0.96), positive predictive value of 0.86 (95% CI: 0.76-0.93) and negative predictive value of 0.49 (95% CI: 0.41-0.54) (Table IV).

Discussion

Cerebral vasospasm leading to late onset ischemic stroke is one of the serious complications of SAH and is one of the leading causes of increased morbidity and mortality. Hence, early diagnosis and management of the vasospasm after SAH is an important step to improve prognosis[12]. The objective of the study was to determine the value of TCD in early diagnosis and monitoring of cerebral vasospasm after SAH, thereby, preventing and treating promptly with the aim of avoiding complications of late-onset cerebral infarction.

Our research showed that SAH was mainly due to ruptured cerebral aneurysm, in which anterior circulation aneurysm is predominant. This result was completely consistent with previous reports from various institutions in developed countries[12,13]. Lindner et al[14] also demonstrated that SAH was mainly caused by the rupture for aneurysms in the anterior cerebral circulation because genetic factors affecting the aneurysm wall structure of the anterior cerebral circulation were different from those of the posterior cerebral circulation.

The study also showed that vasospasm following aSAH was more common in patients with higher HHS and MFS scores. This finding re-

Table IV. Value of TCD and clinical symptoms in the diagnosis of cerebral vasospasm.

	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive predictive value % (95% CI)	Negative predictive value % (95% CI)
TCD	0.95 (0.91-0.98)	0.91 (0.85-0.96)	0.94 (0.90-0.97)	0.93 (0.87-0.97)
Hemiplegia	0.34 (0.27-0.41)	0.92 (0.86-0.96)	0.86 (0.76-0.93)	0.49 (0.41-0.54)
Comatose	0.17 (0.11-0.22)	0.95 (0.90-0.98)	0.84 (0.68-0.93)	0.44 (0.37-0.49)
Confusion	0.15 (0.10-0.20)	0.91 (0.84-0.95)	0.70 (0.53-0.83)	0.42 (0.35-0.47)
Somnolence	0.32 (0.24-0.38)	0.73 (0.63-0.80)	0.63 (0.52-0.72)	0.43 (0.34-0.48)
Irritation sign	0.31 (0.24-0.37)	0.47 (0.37-0.55)	0.46 (0.37-0.55)	0.32 (0.24-0.38)
Headache	0.27 (0.24-0.36)	0.22 (0.13-0.28)	0.34 (0.31-0.36)	0.17 (0.15-0.21)
Seizure	0.17 (0.12-0.18)	0.96 (0.91-0.98)	0.86 (0.83-0.90)	0.44 (0.34-0.36)
Fever	0.16 (0.15-0.18)	0.22 (0.13-0.28)	0.22 (0.16-0.28)	0.15 (0.11-0.19)
Nausea and vomiting	0.12 (0.08-0.19)	0.21 (0.13-0.27)	0.18 (0.14-0.27)	0.14 (0.12-0.20)

95% CI: 95% confidence interval.

flects that, the greater the amount of blood in the subarachnoid space is, the higher the risk of vasospasm is. Also, in the studies of Burkhardt et al[15] and Zheng et al[16], the authors concluded that more bleeding in the subarachnoid space increases the release of inflammatory mediators, such as IL-1b, IL-6, and TNF-a. These inflammatory mediators in inflammation cause changes in the blood-brain barrier, causing microvascular and arteriolar constriction, vasospasm thrombosis, and increased neuronal response to ischemia[15,16].

As was also consistent with previous studies[15,17], our study emphasized the advantage of TCD that TCD was an imaging tool that has been used successfully in early detection of vasospasm and predicts the progression of late onset cerebral infarction over time, which can save valuable time and enable intervention timely to reduce complications of vasospasm.

TCD is optimal, convenient, low-cost and easy-to-use tool for the early diagnosis of cerebral vasospasm by measuring mean cerebral blood flow velocity around Willis polygon, especially measuring mean blood flow velocity in middle cerebral artery through the temporal window with sensitivity and specificity over 90% compared with CTA. This in part led to consistency with previous reports[18,19]. In our study, when diagnosing vasospasm in both anterior and middle cerebral arteries, TCD had a high sensitivity and specificity of over 80%. Lysakowski et al[20] synthesized data from 26 studies comparing the diagnostic value of vasospasm on TCD and CTA, but there was not enough clinical data to confirm that TCD can diagnose vasospasm on other vessels well, except from middle cerebral artery. Current study was currently conducted at Bach Mai Hospital, a special class central hospital in Vietnam, along with professional qualifications of doctors and technicians higher than that of other hospitals. This may affect the diagnostic outcome of TCD. Further studies should expand the research area in hospitals of different levels and grades.

Our study has several strengths. This is the first study in Vietnam to evaluate the diagnostic value of cerebral vasospasm of TCD compared with CTA. In addition, the sample size of the study ensures reliability in measuring the sensitivity, specificity, positive and negative predictive value of TCD. On the other hand, some potential limitations should also be noted in this study. Our sample consisted of patients from a large single center with advanced health professionals, meaning no representation of lower health facilities in Vietnam. Although TCD is a convenient method, the results from TCD are highly dependent on the qualification and experience of the physician. A large number of patients with SAH without the transtemporal window were excluded from the study, which can change the study results significantly. Thus, some of our results should be considered in the light of these limitations and further studies are necessary to corroborate our initial observations.

Conclusions

Current results contribute to the fact that TCD is an effective, simple and convenient method to early diagnose cerebral vasospasm following SAH. TCD helps to monitor clinical conditions effectively, thereby saving time to intervene in time with better prognosis of complications of cerebral infarction later. With low cost and high feasibility, our suggestion from the study is that TCD should be widely applied in Vietnam health facilities from central to grassroots levels instead of the use of CTA.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

We thank our colleagues from the Neurology Center (Bach Mai Hospital, Hanoi, Vietnam) who treated study patients during hospitalization and thus laid the foundation for the study and made its completion possible

Funding

This research received no external funding.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Military Medical University.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1) Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Sex, smoking, and risk for subarachnoid hemorrhage. Stroke 2016; 47: 1975-1981.
2) Dorsch NW. Therapeutic approaches to vasospasm in subarachnoid hemorrhage. Curr Opin Crit Care 2002; 8: 128-133.
3) Charpentier C, Audibert G, Guillemin F, Civit T, Ducrocq X, Bracard S, Hepner H, Picard L, Laxenaire MC. Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage. Stroke 1999; 30: 1402-1408.
4) Rabinstein AA, Friedman JA, Weigand SD, McClelland RL, Fulgham JR, Manno EM, Atkinson JL, Wijdicks EF. Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. Stroke 2004; 35: 1862-1866.
5) Suarez JI, Qureshi AI, Yahia AB, Parekh PD, Tamargo RJ, Williams MA, Ulatowski JA, Hanley DF, Razumovsky AY. Symptomatic vasospasm diagnosis after subarachnoid hemorrhage: evaluation of transcranial Doppler ultrasound and cerebral angiography as related to compromised vascular distribution. Crit Care Med 2002; 30: 1348-1355.
6) Van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet 2007; 369: 306-318.
7) Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. Nat Rev Neurol 2014; 10: 44-58.
8) Chen J, Kathuria S, Gandhi D. Imaging Evaluation and Endovascular Treatment of Vasospasm. Schmidek and Sweet Operative Neurosurgical Techniques: Indications, Methods, and Results: Sixth Edition: Elsevier Inc 2012; 1115-24.
9) Malhotra K, Conners JJ, Lee VH, Prabhakaran S. Relative changes in transcranial Doppler velocities are inferior to absolute thresholds in prediction of symptomatic vasospasm after subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2014; 23: 31-36.
10) Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, Wechsler LR, Newell DW, Gomez CR, Babikian VL, Lefkowitz D. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2004; 62: 1468-1481.
11) Anderson GB, Ashforth R, Steinke DE, Findlay JM. CT angiography for the detection of cerebral vasospasm in patients with acute subarachnoid hemorrhage. AJNR Am J Neuroradiol 2000; 21: 1011-1015.
12) Da Silva IRF, Gomes JA, Wachsman A, de Freitas GR, Provencio JJ. Hematologic counts as predictors of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J Crit Care 2017; 37: 126-129.
13) van Gijn J, Rinkel G. Subarachnoid haemorrhage: diagnosis, causes and management. Brain 2001; 124: 249-278.
14) Lindner SH, Bor ASE, Rinkel GJ. Differences in risk factors according to the site of intracranial aneurysms. J Neurol Neurosurg Psychiatry. 2010; 81: 116-118.
15) Burkhardt JK, Chen X, Winkler EA, Weiss M, Yue JK, Cooke DL, Kim H, Lawton MT. Early hemodynamic changes based on initial color-coding angiography as a predictor for developing subsequent symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. World Neurosurg 2018; 109: e363-e73.
16) Zheng VZ, Wong GKC. Neuroinflammation responses after subarachnoid hemorrhage: a review. J Clin Neurosci 2017; 42: 7-11.
17) Mortimer AM, Steinfort B, Faulder K, Bradford C, Finfer S, Assaad N, Harrington T. The detrimental clinical impact of severe angiographic vasospasm may be diminished by maximal medical therapy and intensive endovascular treatment. J Neurointerv Surg 2015; 7: 881-887.
18) Jabbarli R, Gläsker S, Weber J, Taschner C, Olschewski M, Van Velthoven V. Predictors of severity of cerebral vasospasm caused by aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2013; 22: 1332-1339.
19) Kyoi K, Hashimoto H, Tokunaga H, Morimoto T, Hiramatsu K, Tsunoda S, Tada T, Utsumi S. Time course of blood velocity changes and clinical symptoms related to cerebral vasospasm and prognosis after aneurysmal surgery. No shinkei geka Neurological surgery 1989; 17: 21-30.
20) Lysakowski C, Walder B, Costanza MC, Tramèr MR. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm: A systematic review. Stroke 2001; 32: 2292-2298.