Received: 28.11.2013 / **Accepted:** 09.01.2014
DOI: 10.5137/1019-5149.JTN.9914-13.1

Original Investigation

Evaluating the Diagnostic Accuracy of CT Perfusion in Patients with Cerebral Vasospasm After Aneurysm Rupture: A Meta-Analysis

Anevrizma Rüptüründen Sonra Serebral Vazospazmlı Hastalarda BT Perfüzyonun Tanısal Doğruluğunun Değerlendirilmesi: Bir Meta Analiz

Haogeng SUN[1], Hanmei ZHANG[2], Junpeng MA[1], Yi LIU[1], Chao YOU[1]

[1]*Sichuan University, West China Hospital, Department of Neurosurgery, Chengdu, Sichuan, China*
[2]*Sichuan University, West China Hospital, Department of Radiology, Chengdu, Sichuan, China*

Corresponding Author: Chao YOU / E-mail: manshg@126.com, youchao0817@126.com

ABSTRACT

AIM: Computed tomography perfusion (CTP) has recently been used to identify regions of potential ischemia due to cerebral vasospasm, and CTP parameters are able to quantitatively evaluate brain parenchymal perfusion. We performed a meta-analysis as an update of a previous paper published in 2010 and aimed at evaluating the diagnostic accuracy of CTP and CTP parameters for vasospasm after aneurysm rupture.

MATERIAL and METHODS: Relevant articles published between January 2005 and May 2013 were systematically searched for analysis without language restrictions from the PubMed/MEDLINE, Embase, and Cochrane databases. The data of CTP parameters, including CBV, CBF, MTT and TTP, were extracted for analysis, and the pooled sensitivity, specificity, PLR, NLR, DOR and the sROC curve were determined.

RESULTS: Three relevant articles and a total of 98 patients were finally involved in the analysis. The pooled sensitivity, specificity, PLR, NLR, DOR, and AUC of CTP for diagnosing cerebral vasospasm were 94%, 90%, 8.22, 0.06, 141.09, and 0.9802, respectively. Through the evaluation of CTP parameters, MTT had a higher sensitivity (91%) while CBF had a higher specificity (93%).

CONCLUSION: CT perfusion has a great diagnostic value to detect cerebral vasospasm compared with DSA in patients with aneurysmal subarachnoid hemorrhage (aSAH). As CTP parameters, CBF and MTT quantitatively evaluate brain parenchymal perfusion.

KEYWORDS: CTP, CT perfusion, CTP parameters, Vasospasm, Cerebral vasospasm

ÖZ

AMAÇ: Bilgisayar tomografi perfüzyon (BTP) yakın zamanlarda serebral vazospazm nedeniyle potansiyel iskemi bölgelerini tanımlamak için kullanılmıştır ve BTP parametreleri beyin parankim perfüzyonunu kantitatif olarak değerlendirebilir. 2010 yılında yayınlanan daha önceki bir yazının güncelleştirmesi olarak meta analiz yaptık ve anevrizma rüptürü sonrası vazospazm için BTP ve BTP parametrelerinin tanısal doğruluğunu değerlendirmeyi amaçladık.

YÖNTEM ve GEREÇLER: Ocak 2005 ve Mayıs 2013 arasında yayınlanmış ilgili makaleler PubMed/MEDLINE, Embase, ve Cochrane veri tabanlarından dil sınırlaması olmadan sistematik olarak analiz için tarandı. CBV, CBF, MTT ve TTP de dahil olmak üzere BTP parametreleri verileri analiz için çıkarıldı ve toplanmış duyarlılık, özgüllük, PLR, NLR, DOR ve sROC eğrileri belirlendi.

BULGULAR: İlgili üç makale ve toplam 98 hasta analize dahil edildi. Serebral vazospazmın teşhisi için, BPT'nin toplanmış duyarlılık, özgüllük, PLR, NLR, DOR, ve AUC değerleri sırasıyla %94; %90; 8,22; 0,06; 141,09 ve 0,9802 idi. BTP parametrelerinin değerlendirilmesi yoluyla MT için daha yüksek duyarlılık (%91) ve CBF için daha yüksek özgüllük saptandı (%93).

SONUÇ: BTP testinin anevrizmal subaraknoid hemorajili (aSAK) hastalarda serebral vazospazmı belirlemede anjiyografiye kıyasla önemli diyagnostik değeri vardır. BTP parametreleri olan CBF ve MTT beyin parankimi perfüzyonunu kantitatif olarak değerlendirirler.

ANAHTAR SÖZCÜKLER: BTP, BT perfüzyon, BTP parametreleri, Vazospazm, Serebral vazospazm

ABBREVIATIONS: CTP: computed tomography perfusion, **CBV:** cerebral blood volume, **CBF:** cerebral blood flow, **MTT:** mean transit time, **TTP:** time to peak, **PLR:** positive likelihood ratio, **NLR:** negative likelihood ratio, **DOR:** diagnostic odds ratio, **CIs:** confidence intervals, **SROC:** summary receiver-operating characteristic, **DSA:** digital substraction angiography, **aSAH:** aneurysmal subarachnoid hemorrhage.

INTRODUCTION

Cerebral vasospasm represents the leading cause of morbidity and mortality in the patient population that survives the initial hemorrhage. Angiographic vasospasm occurs most frequently 7- 10 days after aneurysm rupture and can be found in 70% of the patients (2,16). Approximately 50% of the patients with angiographic vasospasm will develop ischemic neurologic deficits (17). Early diagnosis and active treatment are regarded as very important in the management to prevent the sequelae of vasospasm and improve the prognosis of the patients (17).

As the current gold standard, digital subtraction angiography (DSA) can straightforwardly and accurately diagnose anatomic narrowing of cerebral arteries. Endovascular treatment and/or intra-arterial injection can then be performed in time when the situation calls for it (17). However, DSA does not have an absolute advantage for vasospasm diagnosis, because it is an invasive technique and cannot completely explain the occurrence of cerebral ischemia. Some patients with severe vasospasm do not have symptoms while others with modest vasospasm have apparent symptoms and even develop infarction (13).

Computed tomography perfusion (CTP), which is a noninvasive and convenient imaging technique, can be useful to identify regions of potential ischemia due to vasospasm (2), and CTP parameters are able to quantitatively evaluate cerebral hemodynamics (11). A previous meta-analysis was published in 2010 and suggested that CTP can detect vasospasm with high diagnostic accuracy, but the author could not analyse each CTP parameter (5). We comprehensively retrieved the related articles again and additionally included CTP parameters for meta-analysis with the purpose of providing an accurate evaluation of CTP and the CTP parameters in detecting vasospasm after aneurysm rupture.

MATERIAL and METHODS

Literature Search

The PubMed/MEDLINE, Embase, and Cochrane were systematically searched from January 2005 to May 2013 by two authors (H.G.S. and J.P.M.). In our search, the terminology expression included "vasospasm", "DSA" or "DS angiography" or "digital subtraction angiography", "CTP" or "PCT" or "CT perfusion" or "perfusion CT" or "computed tomography perfusion" or "perfusion computed tomography", and "subarachnoid haemorrhage" or "subarachnoid hemorrhage". All articles that evaluated CTP for vasospasm diagnosis following aSAH and used DSA as the criterion standard were identified. The relevant articles from all the reference lists were also considered and the included articles had no language restrictions.

Study Selection and Inclusion Criteria

Two authors (H.G.S. and J.P.M.) independently evaluated the titles and abstracts of identified articles after the literature search and excluded the apparently irrelevant articles. Afterwards, full-text searches were performed on the rest of the articles and they were independently assessed by two authors (H.G.S. and H.M.Z.). Through the fore-mentioned process, articles that met the inclusion criteria were finally enrolled for our meta-analysis. The inclusion criteria were the following: (1) all patients with aSAH; (2) all patients who had undergone both CTP and DSA to detect vasospasm; (3) DSA as the reference standard for the diagnosis of vasospasm; (4) the article can provide adequate information for the rebuilding of the fourfold table; (5) all enrolled patients not reported in other publications. The article was excluded if it did not meet our inclusion criteria. Any disagreements were resolved by consensus.

Data Extraction

CTP parameters include cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP); all of these can provide corresponding data to assess the changes of cerebral blood flow. Though there are no standardized thresholds of CTP parameters for the diagnosis of vasospasm, we had also extracted this data for the meta-analysis and showed the threshold of each parameter as extra information (11,17) (Table II).

In this meta-analysis, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (14,15) was used for each enrolled article to assess the bias risk, variation sources, and reporting quality. The QUADAS tool includes 14 items and each item can be rated "yes," "no," or "unclear." The information of the items was extracted.

As statistical data, true positive, false positive, true negative, and false negative were recorded in the fourfold table. However, if these data were not mentioned, we could get them by computing other reported data, such as sensitivity and specificity. Besides the above information, the extracted information also included basic information of study and patients, number of CTP scans and number of regions of interest. Two authors (H.G.S. and H.M.Z.) independently performed the data extraction and any disagreement was resolved by the third author (J.P.M.) (Tables I, II).

Statistical Analysis

The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with 95% confidence intervals (CIs) were calculated. The Cochran-Q and the inconsistency index were performed to test the heterogeneity in the different research studies. The random-effect model of DerSimonian and Laird method was performed to calculate the pooled sensitivities and specificities and DOR when heterogeneity was statistically significant. In addition, if the heterogeneity was not statistically significant, the fix-effect model of Mantel and Haenszel method was performed. In the right conditions, the summary receiver-operating characteristic (SROC) curve would be drawn to evaluate the overall diagnostic accuracy of CTP and the area under the SROC curve with its Q* point would be described too. The abovementioned statistical analyses were performed by using Meta-Disc 1.4 (Clinical Biostatistics Unit, Hospital Ramon y Cajal, Madrid, Spain) (18).

RESULTS

Trial Selection

The initial search yielded 47 articles. Three articles were identified from the previous meta-analysis (5) and one of these (1) was excluded because the authors only enrolled patients with symptomatic cerebrovascular vasospasm. From the 44 remaining articles, 38 articles were excluded by assessing their titles and abstracts. As relevant studies for this analysis, 6 articles underwent full-text search and assessment, and only one article met the inclusion criteria. Three articles were excluded because the reported data could not construct the fourfold tables (6,12,16). Two articles were not included because one was a reduplicated study (8) and one was a conference abstract. With the two articles identified from previous meta-analysis, a total of three articles (10,11,17) were eventually included in this analysis (Figure 1).

Table I: Characteristics of Studies Included in This Meta-Analysis

Reference, year	Country	No. of patients	No. of CTP scans	No. of ROIs	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Sanelli (11), 2011	America	57	57	28	95	70	NA	NA	94
Moftakhar (10), 2006	America	14	23	NA	NA	NA	NA	NA	NA
Wintermark (17), 2006	America	27	35	18	95.1	90.7	71.3	98.7	91.6

***ROIs** = regions of interest; **PPV** = positive predictive value; **NPV** = negative predictive value; **NA** = not applicable.*

Table II: The Diagnostic Accuracy of CTP Parameters for Evaluating Vasospasm Compared with DSA

CTP parameter	Reference, year	Threshold	Sensitivity (%)	Specificity (%)	Accuracy (%)
CBV, mL/100 g	Wintermark (17), 2006	4.4	27.6	74.6	65.4
TTP, seconds	Wintermark (17), 2006	24.4	87	89.2	88.7
CBF, mL/100 g/min	Sanelli (11), 2011	36.5	95	70	94
	Wintermark (17), 2006	44.3	80.5	94.1	91.4
MTT, seconds	Sanelli (11), 2011	5.4	78	70	85
	Wintermark (17), 2006	6.4	95.1	90.7	91.6

***CBV** = cerebral blood volume; **CBF** = cerebral blood flow; **MTT** = mean transit time; **TTP** = time to peak; **NA** = not applicable.*

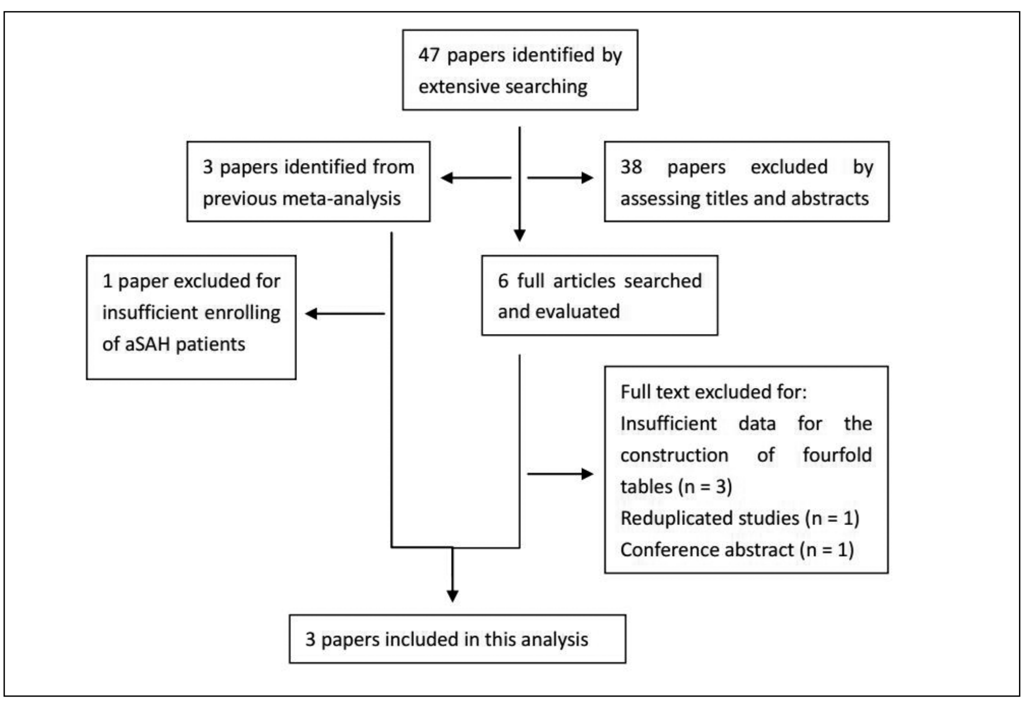

Figure 1: Flow diagram for paper selection.

Quality Assessment

The QUADAS tool, which was used to assess the methodologic quality of all three included studies, revealed several potential biases. One study possibly presented disease-progression bias, because the time intervals between CTP and DSA might be so long that it was hardly sure the vasospasm condition invariant during the wait time (11). In addition, one study did not clearly state that one test was evaluated blinded to the other one and review bias might also have been occurred (17).

Quantitative Analysis of CTP

As only CTP parameters had been studied in two articles, we extracted the statistical data of the CTP parameter, which had the highest diagnostic accuracy of all parameters in the studies, for the CTP analysis (11,17). There were three articles and a total of 98 patients were included. The pooled sensitivity, specificity, PLR, NLR, and DOR of CTP for diagnosing vasospasm following aSAH were 94% (95% CI 0.90–0.97), 90% (95% CI 0.87–0.92), 8.22 (95% CI 6.36–10.62), 0.06 (95% CI 0.03–0.12), and 141.09 (95% CI 66.56–299.06), respectively (Table III). The value of Cochran-Q of DOR was 2.23 (P = 0.3278) and inconsistency index was 10.3%, indicating that there was not significant heterogeneity between the studies. The area under the SROC curve (AUC) was 0.9802 (SE = 0.0098) and the Q* point value was 0.9375 (SE = 0.0185). The SROC curve could not be drawn because only three studies were enrolled for the analysis (Figure 2).

Quantitative Analysis of CTP Parameters

CBF. The analysis of CBF involved 84 patients. The pooled sensitivity, specificity, PLR, NLR, and DOR of CBF threshold values for diagnosing vasospasm after aSAH were 84% (95% CI 0.77–0.89), 93% (95% CI 0.91–0.95), 9.38 (95% CI 6.95–12.66), 0.20 (95% CI 0.14–0.28), and 62.44 (95% CI 35.96–108.42), respectively (Table III). The value of Cochran-Q of DOR was 0.17 (P = 0.6781) and the inconsistency index was 0.0%, showing that there was no significant heterogeneity between the studies. The SROC curve could not be drawn and the AUC with its Q* point could not be described because of the small sample size.

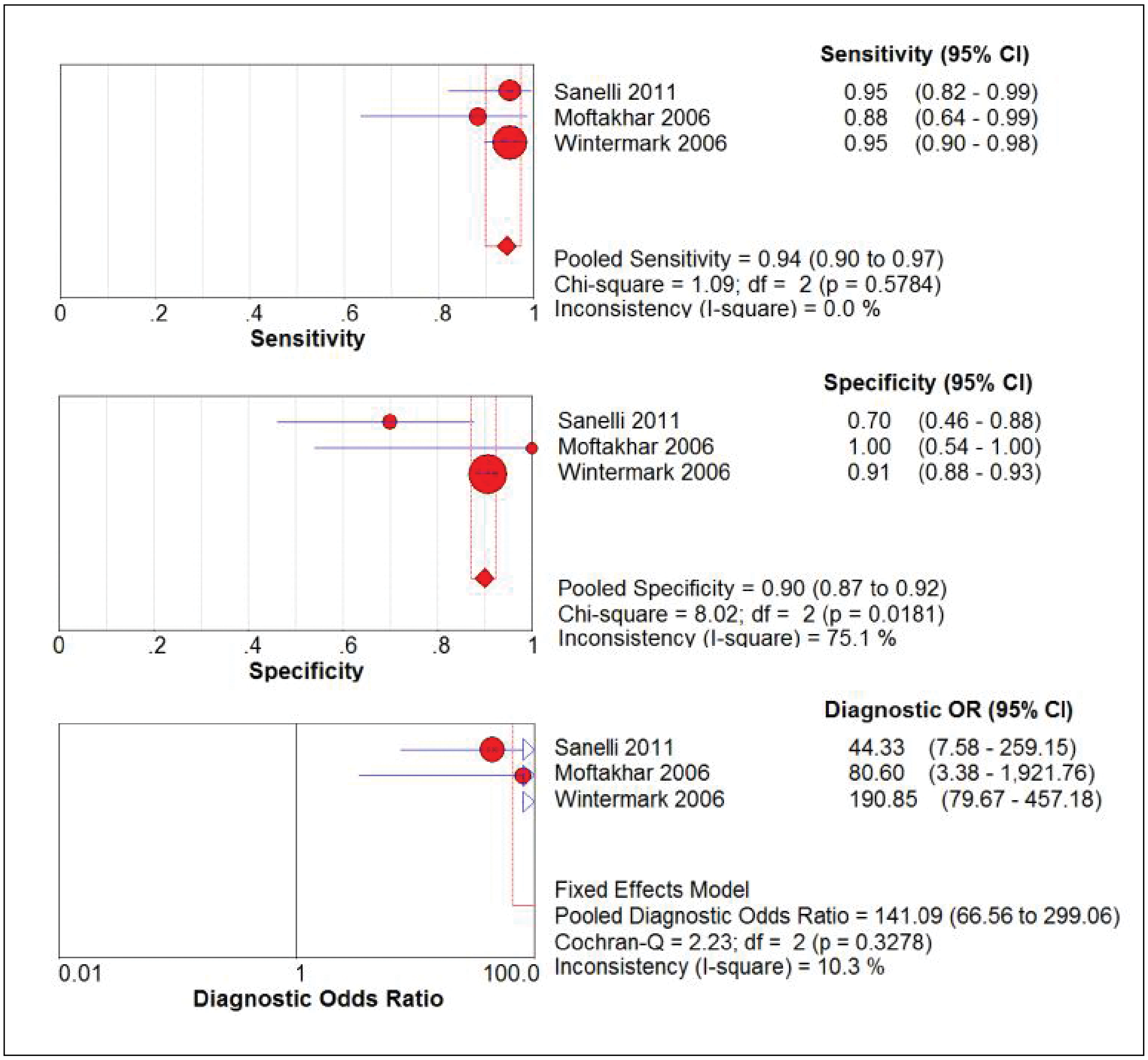

Figure 2: Forest plot of the sensitivity, specificity, and DOR of CTP for detecting cerebral vasospasm after aneurysm rupture.

Table III: Summary of the Analysis Results for CTP and CTP Parameters

	Pooled Sensitivity % (95% CI)	Pooled Specificity % (95% CI)	Pooled PLR (95% CI)	Pooled NLR (95% CI)	Pooled DOR (95% CI)
CTP	94 (90–97)	90 (87–92)	8.22 (6.36–10.62)	0.06 (0.03–0.12)	141.09 (66.56–299.06)
CTP parameter					
CBF	84 (77–89)	93 (91–95)	9.38 (6.95–12.66)	0.20 (0.14–0.28)	62.44 (35.96–108.42)
MTT	91 (86–95)	90 (87–92)	5.34 (1.38–20.76)	0.13 (0.02–1.14)	40.68 (1.85–894.17)

***PLR** = positive likelihood ratio; **NLR** = negative likelihood ratio; **DOR** = diagnostic odds ratio.*

MTT. 84 patients were included in the MTT analysis. The pooled sensitivity, specificity, PLR, NLR, and DOR of MTT threshold values for detecting vasospasm following aSAH were 91% (95% CI 0.86–0.95), 90% (95% CI 0.87–0.92), 5.34 (95% CI 1.38–20.76), 0.13 (95% CI 0.02–1.14), and 40.68 (95% CI 1.85–894.17), respectively (Table III). The value of Cochran-Q of DOR was 16.97 (P = 0.0000) and inconsistency index was 94.1%, showing that the heterogeneity between the studies was proven. Due to the small sample size, the SROC curve and the AUC with its Q* point could not be described.

CBV and TTP. Only one article demonstrated that the CBV threshold values were 4.4 mL/100 g (27.6% sensitivity, 74.6% specificity) and the TTP threshold values were 24.4 seconds (87% sensitivity, 89.2% specificity) (17). Therefore, we could not use the parameters of CBV and TTP for this meta-analysis (Table III).

DISCUSSION

The results of this analysis reveal that CT perfusion has a great diagnostic value to detect cerebral vasospasm compared with DSA in patients with aSAH. Through the evaluation of CTP parameters, both CBF and MTT also show high diagnostic value for the vasospasm detection, and MTT has a higher sensitivity while CBF has a higher specificity.

Some false-positive and false-negative findings could be explained by following causes. First, other pathological conditions, like edema and infection, might also affect cerebral perfusion (3, 4). If the author did not carefully identify the perfusion changes causing by other pathology, the results of CT perfusion could be blurred and false-positive findings were produced. Second, some institutions might not use modern multidetector CT for these studies, and some perfusion disorders, which might be located outside the scanned space, could be hard to detect (1). Third, the beam-hardening artifact, which came from aneurysm clips and coils, might prevent a complete visualization of all arterial segments, and positive results were easily missed (1). Fourth, false-negative findings can result from the assessment of the vertebrobasilar system, because CTP has limitations in evaluating the posterior fossa vascular territories (1,5). In addition, as the time intervals between CTP and DSA were so long, the disease-progression bias could affect the results of comparison and made a lower diagnostic value of CTP (16).

To improve the generalizability of research results, aSAH populations that underwent CTP and DSA should include both asymptomatic and symptomatic patients. In Binaghi's study (1), only patients with symptomatic cerebrovascular vasospasm were enrolled for the analysis, and it reported that the sensitivity and specificity of CTP in detecting vasospasm were 90% and 100%. Although the article met the inclusion criteria of the previous meta-analysis (5), the analysis results were not able to translate all aSAH populations, and we excluded it.

As the absolute CTP parameters, CBV, CBF, MTT and TTP have potential variability caused by the venous output scaling factor and postprocessing steps (7,9). To reduce the variability, the relative CTP parameters including interhemispheric ratios for CBV and CBF, and the interhemispheric differences for MTT and TTP, can be used to evaluate cerebral perfusion (7,9). Unfortunately, the relative CTP parameters were not selected as a research subject for all included articles, and we cannot extract this data for the less variable analysis.

In this meta-analysis, three limitations should be noted: First, as the number of extracted articles is less than 5, the description of the SROC curve could not be realized. As more and more relevant studies are published in the future, we will update the meta-analysis in time. Second, there are no standardized thresholds of CTP parameters for the diagnosis of vasospasm, so a bias was inevitable in the parameters analysis. Third, although we have assessed the diagnostic accuracy of CTP compared with DSA, these two imaging techniques are assessing different parameters. CTP is used to assess brain parenchymal perfusion, and DSA can evaluate the anatomic narrowing of cerebral arteries. Hence, the perfusion disorders at the microcirculatory level may show positive findings on CTP and normal findings on DSA (5,16).

CONCLUSIONS

CTP represents an accurate imaging test for suspected cerebral vasospasm in patients with aSAH. As CTP parameters, both CBF and MTT can quantitatively evaluate brain parenchymal perfusion, and MTT has a higher sensitivity while CBF has a higher specificity. As there are no standardized thresholds of CTP parameters for the diagnosis of vasospasm, a large clinical trial should be performed and these standardized thresholds should be defined in the future.

ACKNOWLEDGEMENT

This article is supported by the National Natural Science Foundation of China (No. 30801185).

REFERENCES

1. Binaghi S, Colleoni M, Maeder P, Uske A, Regli L, Dehdashti AR, Schnyder P, Meuli R: CT angiography and perfusion CT in cerebral vasospasm after subarachnoid hemorrhage. AJNR Am J Neuroradio 28:750-758, 2007
2. Connolly ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS: Guidelines for the management of aneurysmal subarachnoid hemorrhage. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 43:1711-1737, 2012
3. Dankbaar JW, de Rooij NK, Rijsdijk M, Velthuis BK, Frijns CJ, Rinkel GJ, van der Schaaf IC: Diagnostic threshold values of cerebral perfusion measured with computed tomography for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Stroke 41:1927-1932, 2010
4. Dankbaar JW, de Rooij NK, Velthuis BK, Frijns CJ, Rinkel GJ, van der Schaaf IC: Diagnosing delayed cerebral ischemia with different CT modalities in patients with subarachnoid hemorrhage with clinical deterioration. Stroke 40:3493-3498, 2009
5. Greenberg E, Gold R, Reichman M, John M, Ivanidze J, Edwards AM, Johnson CE, Comunale JP, Sanelli P: Diagnostic accuracy of CT angiography and CT perfusion for cerebral vasospasm: A meta-analysis. AJNR Am J Neuroradio 31:1853-1860, 2010
6. Kanazawa R, Kato M, Ishikawa K, Eguchi T, Teramoto A: Convenience of the computed tomography perfusion method for cerebral vasospasm detection after subarachnoid hemorrhage. Surg Neurol 67:604-611, 2007
7. Kealey SM, Loving VA, Delong DM, Eastwood JD: User-defined vascular input function curves: Influence on mean perfusion parameter values and signal-to-noise ratio. Radiology 231:587-593, 2004
8. Killeen RP, Mushlin AI, Johnson CE, Comunale JP, Tsiouris AJ, Delaney H, Dunning A, Sanelli PC: Comparison of CT perfusion and digital subtraction angiography in the evaluation of delayed cerebral ischemia. Acad Radiol 18:1094-1100, 2011
9. Konstas A, Goldmakher G, Lee TY, Lev MH: Theoretic basis and technical implementations of CT perfusion in acute ischemic stroke. Part 2: Technical implementations. AJNR Am J Neuroradio 30:885-892, 2009
10. Moftakhar R, Rowley HA, Turk A, Niemann DB, Kienitz BA, Van Gomple J, Baskaya MK: Utility of computed tomography perfusion in detection of cerebral vasospasm in patients with subarachnoid hemorrhage. Neurosurg Focus 21:1-5, 2006
11. Sanelli PC, Ugorec I, Johnson CE, Tan J, Segal AZ, Fink M, Heier LA, Tsiouris AJ, Comunale JP, John M: Using quantitative CT perfusion for evaluation of delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. AJNR Am J Neuroradio 32:2047-2053, 2011
12. Sviri GE, Britz GW, Lewis DH, Newell DW, Zaaroor M, Cohen W: Dynamic perfusion computed tomography in the diagnosis of cerebral vasospasm. Neurosurgery 59:319-325, 2006
13. Vergouwen MD, Vermeulen M, van GJ, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG: Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies proposal of a Multidisciplinary Research Group. Stroke 41:2391-2395, 2010
14. Whiting PF, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J: The development of QUADAS: A tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 3:25, 2003
15. Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J: Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. BMC Med Res Methodol 6:9, 2006
16. Wintermark M, Dillon WP, Smith WS, Lau BC, Chaudhary S, Liu S, Yu M, Fitch M, Chien JD, Higashida RT: Visual grading system for vasospasm based on perfusion CT imaging: Comparisons with conventional angiography and quantitative perfusion CT. Cerebrovasc Dis 26:163-170, 2008
17. Wintermark M, Ko NU, Smith WS, Liu S, Higashida RT, Dillon WP: Vasospasm after subarachnoid hemorrhage: Utility of perfusion CT and CT angiography on diagnosis and management. AJNR Am J Neuroradio 27:26-34, 2006
18. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A: Meta-DiSc: A software for meta-analysis of test accuracy data. BMC Med Res Methodol 6:31, 2006