Vasospasm on transcranial Doppler is predictive of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis

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OBJECTIVE The impact of transcranial Doppler (TCD) ultrasonography evidence of vasospasm on patient-centered clinical outcomes following aneurysmal subarachnoid hemorrhage (aSAH) is unknown. Vasospasm is known to lead to delayed cerebral ischemia (DCI) and poor outcomes. This systematic review and meta-analysis evaluates the predictive value of vasospasm on DCI, as diagnosed on TCD.

METHODS MEDLINE, Scopus, the Cochrane trial register, and clinicaltrials.gov were searched through September 2014 using key words and the terms “subarachnoid hemorrhage,” “aneurysm,” “aneurysmal,” “cerebral vasospasm,” “vasospasm,” “transcranial Doppler,” and “TCD.” Sensitivities, specificities, and positive and negative predictive values were pooled by a DerSimonian and Laird random-effects model.

RESULTS Seventeen studies (n = 2870 patients) met inclusion criteria. The amount of variance attributable to heterogeneity was significant ($I^2 > 50\%$) for all syntheses. No studies reported the impact of TCD evidence of vasospasm on functional outcome or mortality. TCD evidence of vasospasm was found to be highly predictive of DCI. Pooled estimates for TCD diagnosis of vasospasm (for DCI) were sensitivity 90% (95% confidence interval [CI] 77%–96%), specificity 71% (95% CI 51%–84%), positive predictive value 57% (95% CI 38%–71%), and negative predictive value 92% (95% CI 83%–96%).

CONCLUSIONS TCD evidence of vasospasm is predictive of DCI with high accuracy. Although high sensitivity and negative predictive value make TCD an ideal monitoring device, it is not a mandated standard of care in aSAH due to the paucity of evidence on clinically relevant outcomes, despite recommendation by national guidelines. High-quality randomized trials evaluating the impact of TCD monitoring on patient-centered and physician-relevant outcomes are needed.

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KEY WORDS aneurysmal subarachnoid hemorrhage; cerebral vasospasm; meta-analysis; delayed cerebral ischemia; transcranial Doppler; vascular disorders; mean flow velocity

CEREBRAL vasospasm is a major cause of poor outcomes in aneurysmal subarachnoid hemorrhage (aSAH), resulting in cerebral ischemia, infarction, disability, and death.^{20,25} Cerebral vasospasm is noted on angiography in as many as 70% of patients following aSAH and is predicted by high mean flow velocities (MFVs) on transcranial Doppler (TCD) ultrasonography.^{19,24,26,35} Vasospasm is strongly associated with delayed cerebral ischemia (DCI)¹² and cerebral infarction,^{11,39,49} although poor

outcomes can still occur in its absence. Of the current techniques available for diagnosing cerebral vasospasm, catheter angiography and CT angiography are invasive, and require contrast-dye injection and radiation exposure, and therefore do not allow dynamic monitoring of vasospasm.³¹ The radiation exposure and invasive nature of angiography implies that it is not useful for identifying subclinical vasospasm prior to the onset of the condition, and that its use is frequently restricted to confirm prevalent vasospasm

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; CI = confidence interval; DCI = delayed cerebral ischemia; df = degrees of freedom; MFV = mean flow velocity; MWE = mean weighted estimate; NPV = negative predictive value; PPV = positive predictive value; TCD = transcranial Doppler.

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in patients who have already progressed to a symptomatic status. Therefore, despite knowledge that vasospasm can be fatal after aSAH and despite available treatments, opportunities to reduce the incidence of symptomatic vasospasm are lost, and it is often left untreated because it frequently remains undetected by the providers.⁵² TCD, on the other hand, provides a noninvasive, safe, and bedside modality for dynamic assessment and monitoring of vasospasm. Unlike angiography, TCD can predict symptomatic vasospasm and has high sensitivity, specificity, and positive and negative predictive value.^{16,19,24,26,35}

Although approved and recommended by the American Heart Association/American Stroke Association (rated Class IIA/Level B evidence), American Academy of Neurology, and Neurocritical Care Society (moderate quality evidence/strong recommendation) as a safe and effective modality for noninvasive daily monitoring in aSAH, lack of knowledge of the impact on patient-centered outcomes (disability, quality of life, stroke, mortality, etc.) and weak strength of evidence has prevented it from becoming mandated as a standard of care.^{5,7,43} Consequently, this lack of quality evidence has led to inconsistent and unpredictable utilization of this important resource in neurological intensive care units.^{4,21,28} No prior systematic reviews/meta-analyses have addressed the impact of TCD evidence of vasospasm on patient-centered outcomes. This systematic review and meta-analysis sought to evaluate the clinical impact and predictive value of TCD evidence of vasospasm with the hypothesis that TCD evidence of vasospasm impacts clinical outcomes (i.e., DCI, functional outcome, and mortality).

Methods

A predesigned protocol was used for a search of the literature, study selection, data synthesis, and sensitivity analysis, adhering closely to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.⁴⁵

Search Strategy and Study Selection

MEDLINE, Scopus, the Cochrane Library, and clinicaltrials.gov were searched through September 2014 to identify relevant studies in the literature with the following key words and terms: “subarachnoid hemorrhage,” “aneurysm,” “aneurysmal,” “cerebral vasospasm,” “vasospasm,” “transcranial Doppler,” and “TCD.” Titles and abstracts were screened and articles retrieved if they were relevant or if there was uncertainty. Bibliographies of identified studies as well as relevant reviews in the field were manually searched for potentially eligible studies. Full texts were reviewed when a decision about inclusion could not be made by screening the title and abstract. All study designs (retrospective and prospective) were allowed. Observational studies reporting at least 10 consecutive patients were included. Studies reporting on TCD vasospasm where data pertaining to at least 1 relevant outcome (DCI, functional outcome, or mortality) could not be parsed were excluded. Studies that did not report velocities in cm/sec were excluded. Studies that reported fewer than 10 patients with aSAH, regardless of the total number of patients in the study, were excluded. Other exclu-

sion criteria were as follows: publication of abstracts only, case reports, letters, comments, reviews, or meta-analyses only; animal studies; languages other than English; duplicate studies; no intervention of interest (TCD); lack of outcomes of interest (DCI, functional outcome, or mortality); and not the population of interest (only adults > 18 years old). Studies were also excluded if data pertaining to sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were lacking for any outcome of interest.

Data Extraction and Study Quality

Two authors (G.K. and R.B.S.) independently abstracted data into a standard data form. Data pertaining to sensitivity, specificity, PPV and NPV, DCI, mortality, and functional outcome were extracted. After ensuring accuracy of the extracted data, the 2 data forms were merged into a single form. Study authors were not contacted for clarification and unpublished data or data from abstracts were not sought.

TCD evidence of vasospasm was defined as MFV $\geq$ 120 cm/sec¹ and Lindegaard ratio $\geq$ 3.²³ If the study used another definition of vasospasm but where data were available, TCD vasospasm was recalculated as MFV $\geq$ 120 cm/sec. When no data were available to recalculate MFV, the definition of vasospasm in the study was followed. Angiographic confirmation was not required. DCI was defined as clinical or radiological (CT/MRI) evidence of ischemia.⁵⁰ Functional outcome was defined as alive and independent at follow-up. Any follow-up from 30 days to 6 months was allowed.

In addition, data pertaining to trial quality and design were extracted and tabulated. All studies were evaluated for quality using a 6-category scoring system (0–6).¹⁷ The categories were: 1) definitions of inclusion and exclusion criteria; 2) reported aSAH severity; 3) aSAH severity defined by a standard grading system (for example, the Fisher scale); 4) DCI clearly defined; 5) TCD vasospasm defined; and 6) reported functional outcome/mortality. For each item, studies received a score of 1 if the study fulfilled the criteria and 0 otherwise. Since the focus of the study was to evaluate the impact of TCD evidence of vasospasm on clinical outcomes, data pertaining to angiographic confirmation were not sought.

Statistical Analysis

Publication Bias

Publication bias was evaluated with Begg’s and Egger’s tests (significance defined as $p < 0.05$).^{2,10} Funnel plots were generated for visual appraisal of publication bias. Trim and fill algorithm analysis was planned a priori for adjusting the effect of publication bias on the pooled estimate^{9,37} in the event that publication bias was significant.

Heterogeneity

Heterogeneity between the studies was calculated using the chi-square test for heterogeneity (Cochran Q test). A p value < 0.5 , corresponding to $Q >$ degrees of freedom (df), was regarded as significant for detection of statistical heterogeneity. Heterogeneity was quantified using I^2 ($I^2 =$

$[Q-df] \times 100/Q$, where $df = k-1$, Q = Cochran Q , k = number of studies,¹⁸ and between-study variance expressed as τ^2 . Significant heterogeneity was regarded as $I^2 > 50\%$.

Data Synthesis

Data were transformed to Fisher's z and standard errors calculated. These were then transformed back during meta-analysis, yielding mean weighted estimates (MWEs) with 95% confidence intervals (CIs). A DerSimonian and Laird random-effects model was used to synthesize data for all analyses (the random-effects model defaulted to a fixed-effects model when heterogeneity was absent).⁶ Forest plots were generated to illustrate synthesis. Pooled estimates were expressed as MWEs and 95% CIs.

Sensitivity Analyses

Sensitivity analyses were planned a priori to account for heterogeneity. Subgroup syntheses were performed based on the definition of DCI (clinical vs radiological). A quality score was used for a priori–designed sensitivity analysis for study bias integration. A quality score was incorporated into the synthesis in Doi and Thalib's quality-effects regression model, yielding quality-adjusted pooled estimates.⁸ To test the robustness of the syntheses, exclusion sensitivity analysis was performed to evaluate the extent to which each trial influenced the result of the synthesis. For this analysis each study was excluded, one at a time, and the combined value without a particular

study calculated. All analyses were performed on Mix 2.0 Pro statistical package (BiostatXL).

Results

The search strategy and study selection are outlined in the flow diagram (Fig. 1). Seventeen studies ($n = 2870$ patients) met inclusion criteria.^{3,13,15,16,22,27,29,30,33,34,39–41,44,46,47,51} Study characteristics are summarized in Table 1. No studies addressed the comparative impact of TCD vasospasm on functional outcome and mortality. Only 5 studies used the Lindegaard ratio for defining TCD vasospasm.^{15,27,34,40,41} Therefore, to maintain comparability across studies, MFV alone was used to define vasospasm on TCD. No publication bias was found in any synthesis except for the synthesis of NPV ($p = 0.03$, Begg's test). The amount of variance attributable to heterogeneity was significant ($I^2 > 50\%$) for all syntheses. TCD vasospasm was found to predict DCI with high sensitivity (90%) and NPV (92%), fair specificity (71%), and poor PPV (57%; Table 2). Funnel and forest plots are shown in Figs. 2 and 3, respectively.

Sensitivity Analysis

Estimates were robust to quality adjustment. Subgroup analysis, based on how DCI was defined (clinically vs radiologically), explained heterogeneity. Trends in τ^2 explained and accounted for heterogeneity. Studies that defined DCI radiologically were identified as a source of het-

FIG. 1. Flowchart of the literature search and study selection. TCCS = transcranial color-coded sonography.

TABLE 1. Study characteristics

Authors & Year	Design	DCI Definition	MFV Cutoff*	Inclusion/Exclusion Defined	Reported aSAH Severity	Standardized Severity Scale Used	Defined DCI	Defined Vasospasm	Functional Outcome/Mortality	Quality Score†
Grosset et al., 1992	Pro	Clinical	120	0	1	1	0	1	0	3
Vora et al., 1999	Pro + retro	Clinical	120	1	0	0	1	1	0	3
Rätsep & Asser, 2001	Pro	Clinical ± CT	120	0	1	1	1	1	1	5
Suarez et al., 2002	Retro	Clinical	120	1	1	1	1	1	0	5
Mascia et al., 2003	Pro	Clinical ± angio	160	1	1	1	1	1	0	5
Rabinstein et al., 2004	Retro	CT	120	1	1	1	1	1	1	6
Smith et al., 2005	Retro	Clinical	120	1	1	1	1	1	0	5
Naval et al., 2005	Retro	Clinical	120	1	1	0	1	1	1	5
Sviri et al., 2006‡	Retro	Clinical	70	1	1	1	1	1	0	5
Lee et al., 2006	Retro	CT	120	1	1	1	1	1	0	5
Gonzalez et al., 2007	Retro	Clinical	120	1	1	1	1	1	0	5
Fontanella et al., 2008	Pro	CT	120	0	1	1	1	1	0	4
Carrera et al., 2009 [§]	Retro	Clinical or CT	120	1	1	1	1	1	0	5
Nakae et al., 2011	Retro	Clinical or CT	125	1	1	1	1	1	1	6
Miller et al., 2011	Retro	CT	120	1	1	1	1	1	0	5
Sebastian et al., 2013§	Pro	Clinical	120, 150	1	1	1	1	1	0	5
Malhotra et al., 2014	Retro	Clinical + angio	120	1	1	1	1	1	0	5

Angio = angiography; pro = prospective; retro = retrospective.

* For diagnosis of vasospasm on TCD.

† For each quality metric, the item received a score of 1 if the study fulfilled the criterion and 0 otherwise. The quality score was obtained by a sum of the individual scores in the row. The quality score is integrated into the regression to obtain quality-adjusted estimates (Table 2).

‡ The only study on basilar artery vasospasm.

§ Three criteria were used: 1) baseline middle cerebral artery (MCA) MFV ≥ 120 cm/sec, 2) MCA MFV ≥ 150 cm/sec before angiography, and 3) ratio of MCA MFV before angiography/baseline MCA MFV ≥ 1.5.

erogeneity. Quantifiable heterogeneity did not disappear in the analysis of the subgroup that defined DCI clinically. Inclusion of radiography and angiography in the DCI definition by some of these studies is the likely explanation for persistent variance attributable to heterogeneity. Syntheses for all outcomes were robust to the exclusion sensitivity analysis, and exclusion of no single study influenced the significance of the pooled estimates.

Discussion

Our study is the first systematic review and meta-analysis in the literature that addresses the impact of TCD evidence of vasospasm on DCI, a clinically relevant out-

come event in aSAH. We found that TCD evidence of vasospasm predicts DCI with high sensitivity, high NPV, and fair specificity. Our failure to find studies that address the impact of TCD monitoring on functional outcome and mortality underscores the need for patient-centered trials on comparative effectiveness of TCD. Our results indicate that vasospasm diagnosed on TCD can accurately predict DCI. High sensitivity and NPV make it ideal as a monitoring device, given low false negatives and a high probability that patients with a negative TCD truly have a low likelihood of developing DCI.

A large prospective study of TCD monitoring in aSAH came to this conclusion:⁵²

TABLE 2. Pooled unadjusted and quality-adjusted estimates

Outcome	I ² (%)	τ ²	MWE (95% CI)	MWE (95% CI)				τ ²	
				Quality-Adjusted	Excluding BA Study	Radiological	Clinical	Radiological	Clinical
Sensitivity	99.3	0.89	90% (77–96)	89% (88–90)	91% (78–96)	92% (58–99)	89% (76–95)	0.89	0.61
Specificity	98.5	0.48	71% (51–84)	74% (72–76)	71% (50–84)	71% (–1.5 to 95)	71% (56–81)	0.85	0.19
PPV	97.4	0.24	57% (38–71)	57% (54–60)	57% (37–72)	61% (19–85)	54% (39–67)	0.28	0.12
NPV*	99.0	0.65	92% (83–96)	91% (90–92)	92% (83–96)	93% (64–99)	91% (83–96)	0.81	0.38

BA = basilar artery; I² = percentage of total variance attributable to heterogeneity; τ² = between-study variance.

* Publication bias was significant on Begg's test (p = 0.03) but not Egger's test. Trim and fill correction yielded publication bias-adjusted MWE of 94% (95% CI 94%–95%).

FIG. 2. Funnel plots for the syntheses of sensitivity (A), specificity (B), PPV (C), and NPV (D). Publication bias was not significant except for the synthesis of NPV ($p = 0.03$, Begg's test). Each study is represented by a single equally sized dot. With pseudo-CIs integrated into the plot (orange lines), it can be used to assess how heterogeneous the studies are and which studies are relative outliers. Inverse standard error is on the y-axis, and a measure of effect size (correlation coefficient [cc]) is on the x-axis. Figure is available in color online only.

A routine TCD service provided by neuroradiographers is accurate and useful in diagnosing and managing elevated blood velocities and ischemic neurological deficit following SAH. In addition, it is possible that if the information gleaned from TCD findings was used more often in patient management, outcome might be improved; however, a randomized controlled trial is necessary to assess both these points definitively.

The study demonstrated that TCD was able to predict the subsequent development of symptomatic vasospasm and make a positive contribution to the diagnosis of vasospasm in 72% of patients.⁵² Our results suggest that poor clinical outcomes are potentially avoidable if vasospasm can be identified and treated before permanent cerebral injury sets in. Specific treatments to prevent and treat symptomatic vasospasm include nimodipine, hyperdynamic therapy with induced hypertension, augmentation of cardiac output using inotropic drugs, and intraarterial treatments such as luminal angioplasty and infusions of vasodilators such as nimodipine, verapamil, and milrinone.^{14,32,36,38,42} Despite knowledge that these treatments are effective against vasospasm, these are underutilized due to the absence of real-time monitoring that may detect vasospasm in the presymptomatic phase. With daily TCD monitoring these specific treatments could begin earlier to not only treat symptomatic vasospasm but also prevent va-

sospasm from advancing to the symptomatic phase. Due to lack of direct evidence of impact on clinical outcomes, TCD monitoring is inconsistent and highly variable from institution to institution, and even within an institution among different providers. Therefore, equipoise still exists with regard to TCD monitoring in aSAH.

We posit that the evidence can be strengthened by conducting comparative effectiveness studies of TCD monitoring in aSAH. We believe the key is to design a pragmatic randomized study that tests relevant patient-centered and physician-centric outcomes with and without TCD monitoring. The focus of such work could be to establish that the use of TCD can shorten the time to diagnosis of subclinical and clinical vasospasm and improve outcomes relevant to patients and physicians such as timing of therapy, duration of intensive care unit stay, exposure to contrast agents/radiation, avoidance of ischemic injury, etc. The findings of our systematic review and meta-analysis highlight the need for future studies to evaluate the effectiveness of daily TCD monitoring on patient-centered outcomes in aSAH.

A previous systematic review/meta-analysis did not address the clinical impact of TCD evidence of vasospasm and was focused on correlation with angiographic vasospasm.²⁴ Our study has various methodological strengths.

FIG. 3. Forest plots for the syntheses of sensitivity (A), specificity (B), PPV (C), and NPV (D). cc = correlation coefficient. Figure is available in color online only.

Unlike the previous meta-analysis, our study employed appropriate statistical methods to address the issues of publication bias, study quality, and heterogeneity. We performed a priori–designed subgroup analyses and identified that the way DCI was defined (i.e., clinical vs radiological) explained heterogeneity. Heterogeneity was lower in the subgroup that used a clinical definition of DCI and greater in the subgroup that used radiological/angiographic means to diagnose DCI. This finding uncovers the variation in the definitions used for diagnosing DCI in the literature and highlights the need for future studies to consistently follow a consensus definition of DCI.⁵⁰ To adjust for heterogeneity from variation in quality across studies, we performed quality adjustment that did not sizably change the pooled estimates of sensitivity, specificity, PPV, and NPV. We evaluated and accounted for publication bias, a major threat to the validity of observational study meta-analyses. Publication bias was not significant except in the synthesis of NPV, for which trim and fill correction led to tighter CIs. We demonstrated robustness of our pooled estimates with exclusion sensitivity analysis.

Our study has several limitations. Observational studies lack the inherent bias elimination fail-safe of randomization. Meta-analyses of randomized trials are based on the assumption that each trial provides an unbiased estimate of treatment effect, with the variability between study re-

sults attributable to random variation. Conversely, observational studies yield estimates that may deviate from true underlying relationships beyond the incidence of chance. A meta-analysis of such studies has the potential for bias. However, thorough consideration of possible sources of heterogeneity between study results provides more insights than the mechanistic calculation of an overall measure of effect, which could be biased.

Although we attempted to adhere closely to the consensus definition of DCI,⁵⁰ because most studies included in the analysis were published prior to the publication of the consensus guideline, studies that used definitions that did not strictly conform to the recommendation were also included (Table 1). This serves to account for heterogeneity. We had to exclude the Lindegaard ratio as a diagnostic criterion for vasospasm because most studies did not use it. Instead, to ensure comparability we used the MFV of 120 cm/sec as the cutoff for diagnosis used by most studies. This is a drawback of our study because distinction between vasospasm and hyperemia is reliably made only with calculation of the Lindegaard ratio. We did not seek angiographic confirmation of vasospasm and used TCD evidence of vasospasm.⁴⁸ The reason for this was 2-fold. First, we sought to evaluate the clinical impact of vasospasm as diagnosed by TCD. The dynamic monitoring capability allowing daily surveillance of asymptomatic

patients (those in subclinical vasospasm), coupled with the physiological information generated that confers on TCD the ability to predict symptomatic vasospasm, make it a unique modality that does not justify nor allow a gold-standard confirmation. Second, since there is still variation in the TCD definition of vasospasm, we used the MFV cutoff that is most widely accepted to allow an apples-to-apples comparison.

Sources of heterogeneity other than the way DCI and vasospasm are defined exist. Variation in the treatment of vasospasm introduces heterogeneity. No guidelines currently exist for the treatment of vasospasm. Induced hypertension and hyperdynamic therapy are variably employed for treatment. Nimodipine and statin use can influence outcomes. The year of publication is a potential source of heterogeneity since health care and technological improvements over time may result in improved outcomes. Country of origin is a source of heterogeneity as practice patterns, guidelines, and protocols vary between countries. Quality metrics other than what this study accounted for are potential sources of heterogeneity. These metrics include variation in the time of outcome assessment, variation in the definition of vasospasm, sonographer skill and experience, severity of subarachnoid hemorrhage, etc. These factors need to be carefully considered when designing a trial to study the impact on outcomes.

Conclusions

TCD evidence of vasospasm is predictive of DCI with high accuracy. Although high sensitivity and NPV make TCD an ideal monitoring device, it is not a mandated standard of care in aSAH due to the paucity of evidence on clinically relevant outcomes despite recommendation by national guidelines. High-quality randomized trials evaluating the impact of TCD monitoring on patient-centered and physician-relevant outcomes are needed.

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Disclosure

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Author Contributions

Conception and design: Kumar. Acquisition of data: Kumar, Bavarsad Shahripour. Analysis and interpretation of data: Kumar. Drafting the article: Kumar. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kumar. Statistical analysis: Kumar. Administrative/technical/material support: Kumar. Study supervision: Kumar, Harrigan.

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