Repeat digital subtraction angiography after a negative baseline assessment in nonperimesencephalic subarachnoid hemorrhage: a pooled data meta-analysis

A systematic review

NICOLAAS A. BAKKER, M.D., PH.D.,1 ROB J. M. GROEN, M.D., PH.D.,1 MAHROUZ FOUMANI, M.D.,1 MAARTEN UYTTENBOGAART, M.D., PH.D.,2 OMID S. ESFIGHI, M.D.,3 JAN D. M. METZEMAEKERS, M.D., PH.D.,1 NATASJA LAMMERS, B.SC.,1 GERT-JAN LUIJCKX, M.D., PH.D.,2 AND J. MARC C. VAN DIJK, M.D., PH.D.1

Departments of 1Neurosurgery, 3Neurology, and 4Radiology, University Medical Center Groningen, University of Groningen, The Netherlands

Object. A repeat digital subtraction angiography (DSA) study of the cranial vasculature is routinely performed in patients with diffuse nonperimesencephalic subarachnoid hemorrhage (SAH) after negative baseline CT angiography (CTA) and DSA studies. However, DSA carries a low but substantial risk of neurological complications. Therefore, the authors evaluated the added value of repeat DSA in patients with initial angiographically negative diffuse nonperimesencephalic SAH.

Methods. A systematic review of the contemporary literature was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Studies from January 2000 onward were reviewed since imaging modalities have much improved over the last decade. A pooled analysis was conducted to identify the detection rate of repeat DSA. In addition, the diagnostic yield of repeat DSAs in a prospectively maintained single-center series of 1051 consecutive patients with SAH was added to the analysis.

Results. An initial search of the literature yielded 179 studies, 8 of which met the selection criteria. Another 45 patients from the authors’ institution were included in the study, providing 368 patients eligible for the pooled analysis. In 37 patients (10.0%, 95% CI 7.4%–13.6%) an aneurysm was detected on repeat DSA. The timing of the repeat DSA varied from 1 to 6 weeks after the initial DSA. The use of 3D techniques was poorly described among these studies, and no direct comparisons between CTA and DSA were made.

Conclusions. Repeat DSA is still warranted in patients with a diffuse nonperimesencephalic SAH and negative initial assessment. However, the exact timing of the repeat DSA is subject to debate.

(http://thejns.org/doi/abs/10.3171/2013.9.JNS131337)

Key Words • subarachnoid hemorrhage • digital subtraction angiography • perimesencephalic hemorrhage • vascular disorders

In 10%–30% of patients with spontaneous subarachnoid hemorrhage (SAH), the cause of bleeding is undetected on initial CT angiography (CTA) and catheter angiography (that is, digital subtraction angiography [DSA]) of the cranial vasculature in the acute phase. This patient group is challenging, as swift detection of the cause of bleeding is mandatory to avoid further complications, such as (often devastating) aneurysm rebleeding.

Three subcategories of SAH patients with initial negative CTA and DSA findings can be identified: 1) patients with typical perimesencephalic SAH, 2) patients with SAH diagnosed based on CSF xanthochromia without SAH on CT, and 3) patients with a diffuse nonperimesencephalic (classic) SAH pattern. As regards the first category, many studies have demonstrated a very low additional diagnostic value for DSA, and evaluation via noninvasive CTA is recommended.4,9,12,17 The same may hold true for the second category of patients with CSF xanthochromia.11,15,18,19 The third category is the most challenging. Probable causes for initially negative findings in these patients may be a thrombosed cerebral aneurysm or severe vasospasm. Studies from the pre-CTA era have shown that a repeat DSA study is valuable in these patients, with a diagnostic yield up to 46%.10,11,18 It is therefore common practice to perform repeat DSA in such patients. Nevertheless, cranial DSA is an invasive procedure that carries a 0.5%–1.8% risk of neurological complications, with permanent deficit in 0.09%–0.5%.3,8,22 In addition, nonneurological complications occur in 0.6% of patients, including groin hematoma, peripheral thromboembolism, transient hypotension, and arteriovenous fistulas.3

Over the last decade, noninvasive imaging techniques

Abbreviations used in this paper: CTA = CT angiography; DSA = digital subtraction angiography; MRA = MR angiography; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SAH = subarachnoid hemorrhage.
of study (for example, randomized controlled trial, observational cohort, and so forth).

University Medical Center Groningen Series

A consecutive cohort of 1051 patients with SAH in the period from January 2005 to December 2011, after the introduction of a 64-multidetector CT scanner and 3D DSA facility at the University Medical Center Groningen, the Netherlands, was assessed. All patient data had been prospectively collected in a database and were retrospectively analyzed. A subgroup of 45 patients (4%) with diffuse nonperimesencephalic (classic) SAH had a negative initial cranial CTA and DSA study. Patients with typical perimesencephalic SAH (n = 76) and those without detectable blood on CT (SAH diagnosis made based on CSF xanthochromia, n = 52) were excluded. No patients were lost to follow-up. The other 878 patients with classic aneurysmal SAH were excluded because the vascular pathology was already demonstrated on the initial CTA or DSA.

Treatment Protocol. A multidisciplinary protocol was followed for all of the patients with SAH. All underwent immediate CTA on admission. If an aneurysm or vascular malformation was detected, treatment was administered as appropriate. In cases of negative CTA in the presence of a classic SAH or in cases of diagnostic doubts, patients underwent DSA within 24 hours. If DSA was negative as well, a repeat DSA study was routinely performed after 14 days. In addition, MRI and MR angiography (MRA) of the neuraxis were performed. A second repeat DSA was not routinely performed. A joint multidisciplinary team of interventional neuroradiologists, vascular neurosurgeons, and vascular neurologists evaluated all imaging results.

Computed Tomography Angiography. All CTA examinations were performed on a 64-multidetector CT machine (Somatom Sensation 64, Siemens Medical Systems) using a standard protocol. Source images were transferred to a remote computer workstation (Odelft Benelux Diagnostic Imaging) for viewing. Two-dimensional maximum intensity projection views and 3D surface-rendered and volume-rendered reconstructions were reformatted from the raw image data on a Vitrea computer workstation by an experienced neuroradiologist.

Digital Subtraction Angiography. Cerebral catheter angiography was performed using the Seldinger technique, with a 4- or 5-Fr introducer in the common femoral artery. Standard 6-vessel angiography with intracranial views (frontal, lateral) was completed using 3D rotational angiography (Visipaque [iodixanol] 270 contrast material, GE Healthcare BV).

Statistical Analysis

Continuous variables were expressed as the means ± standard deviation or the median with a range, and categorical variables were expressed as counts and percentages. The 95% confidence intervals of the proportion were calculated using the Wilson procedure without continuity correction. All analyses were performed using SPSS software (version 20.0, SPSS Inc.).
Results

Pooled Analysis

An initial search of the literature yielded 179 studies (Fig. 1), 8 of which met the inclusion criteria: \(^1,2,5,7,13,15,16,23\) Results for these studies are summarized in Table 1. Three hundred sixty-eight patients, including those from the Groningen series, were eligible for the pooled analysis. In 37 patients (10.0%, 95% CI 7.4%–13.6%), a presumed causative vascular anomaly (an aneurysm in all cases) was detected using repeat DSA.

Literature Review

Four-vessel (4 studies) or 6-vessel (3 studies) DSA was routinely performed (one study did not report the type of DSA performed) together with 3D reconstructions in 5 studies. In none of the studies was repeat CTA directly compared with repeat DSA. One study documented a blinded reassessment of images, in which symptomatic aneurysms were retrospectively seen on the initial CTA or DSA in 3 of 4 patients. The timing of the repeat DSA varied from 1 week up to 6 weeks, but it was not reported in 4 of the 8 studies. Complications of DSA were not reported in most studies. Of note, the delayed detection of an aneurysm had clinical consequences in all patients.

University Medical Center Groningen Series

In our cohort of 45 patients who had undergone repeat DSA 14 days after the initial DSA, no vascular abnormalities were detected. Moreover, MRI and/or MRA of the neuraxis did not reveal any vascular abnormalities. All patients had long-term follow-up, with a median of 38 months (range 3–84 months). One patient had rebleeding 2 months after the initial hemorrhage. At reevaluation, a small middle cerebral artery aneurysm was detected and...
subsequently treated using neurosurgical clipping. In retrospect, the aneurysm could not be detected on either the initial or the repeat DSA after the primary hemorrhage. Two patients (4%) had complications attributable to the repeat DSA: one with reversible sensory symptoms in the left hand, and one with persistent neurological deficits and ischemic lesions revealed by MRI.

Discussion

The current pooled analysis of repeat DSA in 368 patients with diffuse nonperimesencephalic SAH and a negative baseline assessment showed a diagnostic yield of 10.0%. It is essential to exclude a potential cause of bleeding in these patients, as a rebleed could have devastating consequences. Therefore, it has always been common practice to perform repeat DSA. This habit was largely based on studies performed before 2000, in which detection rates up to 46% have been reported with repeat DSA. After 2000, according to our pooled analysis, the detection rates lowered because of the better initial diagnostic yield of improved CTA and 3D DSA techniques. However, given the possible consequences of missing detectable vascular pathology, repeat imaging is still justified in diffuse nonperimesencephalic SAH.

A limitation of our analysis is the heterogeneity of the DSA techniques used in the included studies as well as the variety in the timing of repeat DSA (if it was reported at all). In some centers, 4-vessel instead of 6-vessel DSA was performed. Although their incidence is low, cranial dural arteriovenous fistulas might be missed with 4-vessel DSA. We therefore propose always including projections of the external carotid arteries on the initial DSA.

The timing of repeat DSA is also debatable. This was demonstrated in the study by Dalyai et al., in which the first repeat DSA after 7 days revealed 10 aneurysms, but a second repeat DSA after 6 weeks revealed another 7 patients with a vascular abnormality. Nevertheless, it is difficult to draw any conclusions, as only a few studies have focused on the timing of repeat DSA. Given the vasospasm period and the chance of a thrombosed aneurysm, it is reasonable to perform a repeat DSA at least 10–14 days after the ictus, thereby avoiding the need for a second repeat DSA.

A negative initial DSA study is typically the result of a thrombosed aneurysm or severe vasospasm. In such cases, aneurysms might also be identified using repeat CTA. Although it has been reported that CTA has limitations with regard to small aneurysms located close to the skull base, a recent study on the diagnostic yield of repeat CTA compared with repeat MRA in diffuse nonperimesencephalic SAH revealed the superiority of CTA, with detection of small aneurysms (median 2.6 mm) in 9.3% of patients. Furthermore, the retrospective study by Little et al. showed that 3 of 4 newly discovered aneurysms would have also been detected by CTA. This finding is in line with those in a recent meta-analysis by Westerlaan et al., who demonstrated that high-resolution CTA might be considered an alternative to DSA as the primary imaging tool for detecting cerebral vascular abnormalities. Nevertheless, studies directly comparing repeat CTA and
Repeat digital subtraction angiography—negative SAH

repeat DSA are lacking. Further research on this topic is therefore warranted.

Conclusions

Although detection rates of repeat DSA have lowered over the last decade in patients with diffuse nonperimesencephalic SAH, the diagnostic yield of repeat DSA is still 10.0%. The timing and technique of repeat DSA is debatable. A direct prospective comparison between repeat CTA and repeat DSA is lacking.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bakker, Van Dijk. Acquisition of data: Bakker, Foumani, Lammers. Analysis and interpretation of data: Bakker. Drafting the article: Bakker, Van Dijk. 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: Bakker. Statistical analysis: Bakker. Study supervision: Groen. Performed DSA: Eshghi, Van Dijk.

References


Manuscript submitted June 26, 2013. Accepted September 17, 2013.
Please include this information when citing this paper: published online October 25, 2013; DOI: 10.3171/2013.9.JNS131337.
Address correspondence to: Nicolaas A. Bakker, M.D., Ph.D., Department of Neurosurgery AB71, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. email: n.a.bakker@umcg.nl.