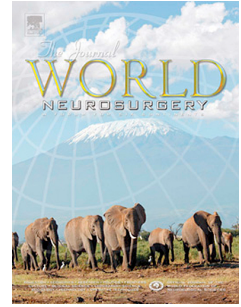


Accepted Manuscript

Results of an International Survey on the Investigation and Endovascular Management of Cerebral Vasospasm and Delayed Cerebral Ischemia

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PII: S1878-8750(15)00058-3

DOI: [10.1016/j.wneu.2015.01.036](https://doi.org/10.1016/j.wneu.2015.01.036)

Reference: WNEU 2690

To appear in: *World Neurosurgery*

Received Date: 27 September 2014

Revised Date: 31 December 2014

Accepted Date: 19 January 2015

Please cite this article as: Hollingworth M, Chen PR, Goddard AJ, Coulthard A, Söderman M, Bulsara KR, Results of an International Survey on the Investigation and Endovascular Management of Cerebral Vasospasm and Delayed Cerebral Ischemia, *World Neurosurgery* (2015), doi: 10.1016/j.wneu.2015.01.036.

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Abstract

Background: Delayed cerebral ischemia (DCI) is a major cause of morbidity and mortality in aneurysmal subarachnoid hemorrhage. Endovascular management of this condition offers a new hope in preventing adverse outcome, however a uniform standard of practice is lacking owing to a paucity of clinical trials. We conducted an international survey on the use of investigative and endovascular techniques in the treatment of DCI in order to assess the variability of current practice. **Methods:** Neurovascular neurosurgeons and neuroradiologists were contacted via professional societies from America, United Kingdom, Europe and Australasia. Members were invited to complete a 13-item questionnaire regarding screening techniques, first- and second-line therapies in endovascular intervention, and the role of angioplasty. Answers were compared using chi-square testing for nonparametric data. **Results:** Data from 344 respondents from 32 countries were analyzed: 167 non-US and 177 US respondents. More than half of all clinicians had more than 10 years of experience in units with a mixture of higher and lower case volumes. Daily transcranial Doppler ultrasonography was the most commonly used screening technique by both US (70%) and non-US (53%) practitioners. Verapamil was the most common first-line therapy in the United States, whereas nimodipine was most popular in non-US countries. Angioplasty was performed by 83% of non-US and 91% of US clinicians in the treatment of vasospasm; however, more US clinicians reported using angioplasty for distal vasospasm. **Conclusions:** Treatment practices for DCI vary considerably, with the greatest variability in the choice of agent for intra-arterial therapy. Our data demonstrate the wide variation of

approaches in use today; however, without further clinical trials and development of a uniform standard of best practice, variability in treatment and outcome for DCI is likely to continue.

ACCEPTED MANUSCRIPT

Results of an International Survey on the Investigation and Endovascular Management of Cerebral Vasospasm and Delayed Cerebral Ischemia

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Cover Title: Cerebral Vasospasm Management: An International Survey

Keywords: cerebral vasospasm; subarachnoid hemorrhage, delayed cerebral ischemia; intra-arterial treatment, transcranial Doppler, angioplasty, survey

Word count: 3175 (+ 4 figures, 1 table and 1 supplemental material)

Abstract

Background: Delayed cerebral ischemia (DCI) is a major cause of morbidity and mortality in aneurysmal subarachnoid hemorrhage. Endovascular management of this condition offers a new hope in preventing adverse outcome, however a uniform standard of practice is lacking owing to a paucity of clinical trials. We conducted an international survey on the use of investigative and endovascular techniques in the treatment of DCI in order to assess the variability of current practice. Methods: Neurovascular neurosurgeons and neuroradiologists were contacted via professional societies from America, United Kingdom, Europe and Australasia. Members were invited to complete a 13-item questionnaire regarding screening techniques, first- and second-line therapies in endovascular intervention, and the role of angioplasty. Answers were compared using chi-square testing for nonparametric data. Results: Data from 344 respondents from 32 countries were analyzed: 167 non-US and 177 US respondents. More than half of all clinicians had more than 10 years of experience in units with a mixture of higher and lower case volumes. Daily transcranial Doppler ultrasonography was the most commonly used screening technique by both US (70%) and non-US (53%) practitioners. Verapamil was the most common first-line therapy in the United States, whereas nimodipine was most popular in non-US countries. Angioplasty was performed by 83% of non-US and 91% of US clinicians in the treatment of vasospasm; however, more US clinicians reported using angioplasty for distal vasospasm. Conclusions: Treatment practices for DCI vary considerably, with the greatest variability in the choice of agent for intra-arterial therapy. Our data demonstrate the wide variation of approaches in use today; however, without further clinical trials and

development of a uniform standard of best practice, variability in treatment and outcome for DCI is likely to continue.

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Introduction

Subarachnoid haemorrhage (SAH) accounts for only 5% of stroke, however it carries considerable mortality of up to 40% (1). This is in part related to phenomena of delayed cerebral ischemia (DCI), which has been reported to occur in 29% of SAH (2). DCI, typically occurring occurring 3-14 days after aneurismal rupture (2), refers to a temporary or permanent focal or global neurological deficit that can result in cerebral infarction and death (3). The pathogenesis of DCI is complex involving cellular, humoral and genetic factors; however, central to its development is cerebral vasospasm (4). 50% of patients with angiographic vasospasm develop delayed ischemic neurological deficits with resultant stroke or death (5-7). So intimately linked are DCI and cerebral vasospasm, that the terms are often used interchangeably (3). Importantly, however, DCI and cerebral vasospasm may occur independently of one another with DCI occurring in the absence of cerebral vasospasm and visa versa (8). Problems with nomenclature have lead to inconsistencies between studies and so, in keeping with contemporary consensus (3), vasospasm will solely be used to describe the angiographic phenomena of cerebrovascular constriction herein. Nevertheless, the outcome for patients suffering DCI is significant. Attempts have been made to improve outcome with various systemic therapies (4), however advances have been made regarding endovascular techniques providing mechanical (9-11) and pharmaceutical splinting of cerebral vasculature (12,13). However, there is a paucity of clinical trials regarding which endovascular therapies deliver superior outcomes, with the neurocritical care community concluding

that too many small, uncontrolled, often retrospective studies provide little definitive guidance on the subject (14). This lack of clarity has given rise to significant variability in practice amongst US endovascular interventionalists (15). We aimed to investigate variability in international practice and compare management strategies between US and non-US clinicians. By analysing data from members of American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Cerebrovascular Section, the British Society of Neuroradiologists (BSNR), the European Society of Neuroradiologists (ESNR), and the interventional section of the Australian and New Zealand Society of Neuroradiology (ANZINC), we compare international perspectives from America, United Kingdom, Europe and Australasia on the management of DCI. By gaining insight into current practice around the world, we aim to explore differences in management strategies and suggest possible hypotheses for future study, which could one day lead to a uniform standard of best practice regarding investigation and endovascular therapy for DCI and cerebral vasospasm.

Methods

A survey was designed and distributed to practitioners worldwide via the AANS/CNS, BSNR, ESNR and ANZINC. Surveys were distributed via e-mail to every active member (Supplementary material 1). The survey consisted of 13 questions on screening techniques, choice of first- and second-line therapies in endovascular intervention, and the role of angioplasty. The responses were collected anonymously. Data collection was conducted among AANS/CNS members in June 2012 (15) and was extended

to the ESNR, BSNR, and ANZINC members in November 2013. Data collection was conducted over a 3-month period and reminder e-mails were sent to all members before the survey deadline. Statistical analysis was undertaken with SPSS Version 21 (IBM Corp, Armonk, NY) for chi-square testing for nonparametric data.

Results

A total of 344 responses were collected from the AANS/CNS, ESNR, BSNR and ANZINC members, from whom we received 177, 102, 32, and 23 responses respectively. The response rates were reported between 16-40%. Responses were subdivided into 177 US and 167 non-US responses. The latter included practitioners from 32 different countries (Table 1).

The proportion of respondents with more than 10 years of experience in practice was not significantly different between the US and non-US respondents (p -value > 0.05). 57% percent of non-US respondents (96/167) and 60% of US respondents (106/177) had more than 10 years of experience, and only 16% (27/167) and 21% (37/177) of non-US and US respondents, respectively, had less than 5 years of experience (Figure 1A). Both groups had high case loads of aneurysmal SAH, although the case load was higher among non-US respondents, with 44% (75/167) reporting more than 100 cases of aneurysmal SAH per year compared with 25% of US respondents (44/177). Only 5% (9/167) and 11% (19/177) of non-US and US respondents, respectively, managed fewer than 25 cases per year (Figure 1B).

Reported screening methods for DCI demonstrated significant variability both between US and non-US countries and within the US itself

(Figure 1C). Daily transcranial Doppler (TCD) ultrasonography was the most commonly used technique overall; 58% of respondents (208/344) reporting using daily TCDs. 53% of non-US respondents (90/167) and 70% of US respondents (123/177) reported using daily TCDs. Computed tomography angiography (CTA) conducted between days 5 and 10 was the next most commonly used screening tool, reported by 15% of respondents (54/344). Routine angiogram at 5 to 10 days was reported by 13% (45/344) of respondents overall. Both routine CTA and angiography were more commonly reported by US than by non-US respondents at 23% (40/177) versus 9% (15/167) and 24% (41/177) versus 5% (8/167), respectively. Other methods of DCI screening included computer tomography perfusion (CTP), magnetic resonance spectroscopy (MRS), magnetic resonance angiography (MRA), digital subtraction angiography (DSA), and electroencephalography (EEG). CTP was used by more than one respondent, which was reported by 5 US and 6 non-US respondents. The differences in use of screening methods between US and non-US respondents were statistically significant in all cases (p -value < 0.05).

In 60% of cases (209/344), practitioners began DCI treatment only if clinical symptoms were present. However, US respondents were more likely to initiate treatment on the basis of radiographic evidence of cerebral vasospasm, with 54% of US respondents (95/177) saying they would do so compared with only 26% of non-US respondents (44/167; Figure 2A; p -value < 0.05). To begin treatment for DCI, 91% of the total respondents (313/344) would maximize critical care management; however, a minority of both US and non-US respondents would proceed straight to endovascular treatment

(Figure 2B). However, 93% of non-US respondents (156/167) and 95% of US respondents (168/177) would use endovascular intervention in the management of DCI (Figure 2C).

Respondents were invited to select their first-line and second-line endovascular therapies from papaverine, milrinone, verapamil, or nimodipine or to enter their own preference. Data were grouped by the respective pharmaceutical agents, including other endovascular therapies commonly volunteered by respondents, which included angioplasty and nimodipine. Other options that were less commonly volunteered such as glyceryl trinitrate and fasudil hydrochloride were grouped under *Other*. Responses to questions that specified endovascular therapy that did not include endovascular therapies were excluded. There was significant variation both within and between groups regarding first-line endovascular therapy (Figure 3A). Among US practitioners, verapamil was used by 56% of respondents (93/168), while nicardipine, papaverine, milrinone, and nimodipine were used by 25% (42/168), 7% (12/168), 3% (5/168), and 3% (5/168), respectively. Other first-line therapies chosen by US respondents included fasudil hydrochloride, angioplasty, and angioplasty in combination with pharmaceutical agents. Among non-US respondents, verapamil was not the most commonly used first-line agent; verapamil was used by only 6% of non-US respondents (9/156). The most common first-line agent chosen by the non-US respondents was nimodipine, which was used by 74% (116/156). Other therapies used by non-US clinicians were nicardipine, milrinone, papaverine, and angioplasty by 3% (5/156), 2% (3/156), 6% (9/156), and 6% (9/156), respectively.

A total of 80% of respondents (277/344) reported using a second-line endovascular therapy, which also varied between countries. For second-line therapies, larger proportions of respondents opted for angioplasty (Figure 3B): 26% (37/143) and 11% (15/134) of respondents in non-US countries and the US, respectively. However, the majority of respondents opted for pharmacological agents. As a second-line therapy, 27% (36/134), 26% (34/134), and 19% (25/134) of US respondents chose verapamil, nicardipine, and papaverine, respectively. Interestingly, 3% of US respondents (4/134) opted to use glyceryl trinitrate; however, only 1 US respondent opted to use nimodipine. Second-line therapies used by non-US respondents included nimodipine, verapamil, papaverine, milrinone, and nicardipine, which were selected by 34% (48/143), 9% (14/143), 19% (27/143), 7% (10/143), and 4% (6/143), respectively (Figure 3B).

Respondents were also asked to describe the association between their first-line endovascular therapy and immediate angiographic effect as “always,” >80%, >50%, <50%, or 10-30%. This was associated with marked variability. However, the reported data suggested that nimodipine was more commonly associated with an immediate angiographic response than was verapamil. 52% (62/117) of responders using nimodipine as a first-line therapy reported an immediate angiographic response always or at least 80% of the time. Only 42% (50/117) of verapamil users, however, reported an immediate response always or at least 80% of the time (Figure 3C). Angioplasty was used by the majority of US and non-US groups, which was reported by 91% (162/177) and 83% (139/167), respectively (Figure 4A). However, 23% of US practitioners (39/168) used angioplasty for distal

vasospasm compared with 6% (8/139) of non-US respondents (Figure 4B), which was a statistically significant difference (p -value < 0.05). In response to the question, “What is the best endovascular therapy for DCI?” the most popular opinion was angioplasty (161/344 of respondents; Figure 4C). 51% (90/167) and 61% (107/177) of non-US and US respondents agreed that treatments involving angioplasty offer superior outcomes, which suggests a prevailing view worldwide that angioplasty is the best treatment for DCI

Discussion

We present the results of an international survey of the management of DCI by both US and non-US practitioners. The majority of responders were experienced clinicians with high numbers of SAH cases per year. We found significant variability between the US and the rest of the world in current practice regarding both screening methods and treatment options. We also found significant variability among US respondents in the first- and second-line therapies chosen.

Our results suggest that screening is more commonly used by US clinicians; however, the use is far from ubiquitous, with only 70%, 23%, and 24% of the total sample using daily TCDs, routine CTA, and routine angiography, respectively. Furthermore, some centers inside and outside the US use different techniques such as CTP, the efficacy of which offers an interesting hypothesis for further study.

The explanation of the disparity between use of screening methods between US and non-US respondents is unclear. Whether it pertains to resource availability or different perspectives on best practice remains to be

seen. Nevertheless the effect of screening methods on the outcome of DCI needs to be further elucidated to ensure a cost-efficient strategy with optimal clinical outcome.

Most US and non-US clinicians agreed that maximal critical care management should be attempted as a first-line therapy. However, again major differences in practice were apparent regarding the use of angioplasty and different intra-arterial pharmaceutical agents. Verapamil was commonly reported as a first-line therapy by US respondents, whereas nimodipine was seldom used. By contrast, most non-US clinicians used nimodipine and verapamil less so. Data regarding the choice and dose of intra-arterial therapy are limited (14). Indeed, according to self-reported data regarding immediate angiographic changes following endovascular intervention, more clinicians saw an immediate angiographic response following nimodipine administration versus verapamil. However, the extent to which this would correlate with clinical outcome is unclear, considering that 82% to 100% of patients have angiographic improvement but 23% to 69% still go on to suffer cerebral ischemia (9-11). Nevertheless, the use of nimodipine versus verapamil presents an interesting and worthwhile hypothesis for study with worldwide implications.

This survey of current practitioners was dependent on self-report. The survey does not represent the practice of all practitioners worldwide and it offers a limited view of current practices. It is difficult to estimate the number of clinics or proportion of clinicians our data represent owing to our method of online survey distribution. Response rate was estimated by AANS/CNS, BSNR, ESNR and ANZINC between 16-40%, however the institutions cited

limitations in calculating response rates owing to many members who are not actively involved in the management of DCI and some respondents answering on behalf of their hospital comprising a number of clinicians. Indeed, this survey also did not account for the different backgrounds of respondents. Endovascular therapies can be utilized by both neurosurgeons and neuroradiologists depending on local policy. It is unclear whether this would affect practice and may offer an interesting avenue of study. Nevertheless, with 344 respondents in 32 different countries, this study offers the most comprehensive insight into contemporary international DCI management practices currently available.

Although we cannot infer efficacy of treatments or suggest protocols for screening methods, this survey suggests several interesting hypotheses for further investigation. This includes how outcome could be affected by using daily TCD and routine vascular imaging techniques, the choice of pharmaceutical agents, and the use of angioplasty. Moving forward, it will be critical to define appropriate and accurate outcome parameters, for registries or prospective trials, to reliably identify which agents or strategies may be superior in the management of DCI.

To this end, we have initiated the Intra-arterial Vasospasm Trial (IVT; NCT01996436 on clinicaltrials.gov). The IVT is an ongoing multicenter randomized trial across America recruiting over 200 patients with DCI refractory to standard hospital care. By random assignment of intra-arterial agents (nicardipine, milrinone, verapamil or a combination of nicardipine, verapamil and nitroglycerin) via endovascular catheter, these patients will form the basis of a randomized trial designed to identify the most efficacious

intra-arterial agents. Primary outcome parameters include changes in post-infusion vessel caliber 10 minutes after agent infusion, while secondary outcome parameters will measure morbidity and mortality using the Modified Rankin score 6 weeks post-hospital discharge. It is a hope that this will mark the beginning of an evidenced based approach to achieve a uniform standard of best practice for the endovascular management of DCI and cerebral vasospasm

Conclusion

344 respondents from 32 different countries offered their expertise regarding the management of DCI providing a comprehensive insight into available practices worldwide. This survey demonstrates important differences in practice both within the United States and compared to the rest of the world. Such variations in screening methods and endovascular therapy should prompt further clinical trials, including the extension of the IVT outside the US, in order to achieve a universally recognized standard of best practice for this challenging therapeutic dilemma.

Acknowledgements

We acknowledge the kind co-operation of AANS/CNS, BSNR, ESNR, and ANZINC for distributing our survey to their members. We would also like to thank Murat Gunel MD for his help in developing this project.

Sources of Funding

No author received funding relevant to this study

Disclosures:

Milo Hollingworth, Peng Roc Chen, Antony JP Goddard, Alan Coulthard, Michael Söderman and Ketan R. Bulsara declare no conflicting interest regarding the design, conduct or analysis of this article

References

1. Lovelock CE, Rinkel GJ, Rothwell PM. Time trends in outcome of subarachnoid haemorrhage: population based study and systematic review. *Neurology*. 2010; 74: 1494-1501
2. Dorsch A. A clinical review of cerebral vasospasm and delayed ischemia following aneurysm rupture. *Acta Neurochir. Suppl.* 2011; 110: 5-6
3. Vergouwen MDI, The participants in the international multi-disciplinary consensus conference on the critical care management of subarachnoid haemorrhage. Vasospasm versus delayed cerebral ischemia as an outcome event in clinical trials and observational studies. *Neurocrit Care*. 2011; 15: 308-311
4. Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. *Nat Rev Neurol*. 2014; 10:44-58.
5. Velat GJ, Kimball MM, Mocco JD, Hoh BL. Vasospasm after aneurysmal subarachnoid hemorrhage: review of randomized controlled trials and meta-analyses in the literature. *World Neurosurg*. 2011;76:446-454.
6. Haley EC, Jr., Kassell NF, Torner JC. The International Cooperative Study on the Timing of Aneurysm Surgery. The North American experience. *Stroke*. 1992;23:205-214.
7. Longstreth WT, Jr., Nelson LM, Koepsell TD et al. Clinical course of spontaneous subarachnoid hemorrhage: a population-based study in King County, Washington. *Neurology*. 1993;43:712-718.

8. Dankbaar JW, Rijndijk M van der Schaaf IC, Velthuis BK, Wermer MJ, Rinkel GJ. Relationship between vasospasm, cerebral perfusion, and delayed cerebral ischemia after aneurysmal subarachnoid haemorrhage. *Neuroradiology*. 2009; 51:813-819
9. Higashida RT, Halbach VV, Cahan LD, et al. Transluminal angioplasty for treatment of intracranial arterial vasospasm. *J Neurosurg*. 1989;71:648-653.
10. Bejjani GK, Bank WO, Olan WJ et al. The efficacy and safety of angioplasty for cerebral vasospasm after subarachnoid hemorrhage. *Neurosurgery*. 1998;42:979-986
11. Coyne TJ, Montanera WJ, Macdonald RL, Wallace MC. Percutaneous transluminal angioplasty for cerebral vasospasm after subarachnoid hemorrhage. *Can J Surg*. 1994;37:391-396.
12. Volk JM, Culichchia F, Dawson R, Use of intra-arterial infusion of calcium-channel blockers through an indwelling microcatheter- one institutions's experience. *Stroke*. 2012; 43: A47
13. Albanese E et al. Ultra high-dose intra-arterial infusion of verapamil through an indwelling microcatheter for medically refractory severe vasospasm: initial experience. *J Neurosurg*. 2010; 113 :913-922
14. Kimball MM, Velat GJ, Hoh BL. Critical care guidelines on the endovascular management of cerebrovasospasm. *Neurocrit Care*. 2011; 15: 336-341
15. Bulsara KR, Günel M, Amin-Hanjani S, Chen PR et al. Results of a national cerebrovascular neurosurgery survey on the management of cerebral vasospasm/delayed cerebral ischemia. [published online

ahead of print date]. *J Neurointerv Surg.* 2014.
<http://jn.is.bmj.com/content/early/2014/05/12/neurintsurg-2014-011223.long>. Accessed June 3, 2014.

Figure legends

Figure 1. A) US (n=177) and non-US (n=167) clinicians reported years experience managing subarachnoid haemorrhage: Less than 5 years (US 21%; non-US 16%), 5-10 years (US 18%; non-US 24%) and over 10 years (US 57%; non-US 60%); B) US (n=177) and non-US (n=167) clinicians reported annual case loads of subarachnoid haemorrhage: less than 25 (US 11%; non-US 5%), 25-50 (US 26%; non-US 20%), 50-100 (US 34%; non-US 34%) and over 100 (US 25%; non-US 44%) cases per year; C) US (n=177) and non-US (n=167) clinicians reported use of delayed cerebral ischemia screening technique: the most common method was daily transcranial Dopplers (US 70%; non-US 53%) other common options included routine computer tomography angiography (between days 5-10) (US 23%; non-US 9%) and routine angiogram (between days 5-10) (US 24%; non-US 5%). Differences between US and non-US countries in use of screening methods met statistical significance in all cases (p-value < 0.05).

Figure 2. A) The difference between US (n=177) and non-US (n=167) responders treating delayed cerebral ischemia on the basis of radiological cerebral vasospasm alone differed with statistical significance (US 54%; Non-US 26%; p-value < 0.05); B) Initial therapy reported by US (n=177) and non-US (n=167) responders most commonly included intensive care treatment (US

91%; Non-US 91%) compared to endovascular therapy (US 9%; Non-US 9%);
 C) The majority of both US (n=177) and non-US (n=167) respondents used endovascular therapy in the treatment of delayed cerebral ischemia (US 93%; Non-US 95%)

Figure 3. A) US (n=168) and non-US (n=156) practitioners reported first-line endovascular therapy: angioplasty (US 3%; non-US 6%), milrinone (US 3%; non-US 2%), nicardipine (US 25%; non-US 3%), nimodipine (US 3%; non-US 74%), papaverine (US 7%; non-US 6%), verapamil (US 56%; non-US 6%) and other agents (US 2%; non-US 0%) including fasudil hydrochloride. B) US (n=134) and non-US (n=142) practitioners reported second-line endovascular therapy: angioplasty (US 11%; non-US 26%), milrinone (US 4%; non-US 7%), nicardipine (US 26%; non-US 4%), nimodipine (US 1%; non-US 34%), papaverine (US 19%; non-US 19%), verapamil (US 27%; non-US 9%) and other agents (US 3%; non-US 0%) including glyceryl trinitrate ; C) US and non-US practitioners (n=324) reported immediate angiographic responses following first-line endovascular therapy as *Always*, *more than 80%*, *more than 50%*, *10-30%* or *Never*. Each endovascular therapy was associated with varying degrees of reported immediate angiographic response.

Figure 4. A) 95% of US (n=177) and 83% of non-US (n=167) responders reported using angioplasty in the management of delayed cerebral ischemia; B) Use of angioplasty for distal cerebral vasospasm was highest amongst US (n=168) respondents at 23% versus 6% for non-US (n=139) respondents; this reached statistical significance (p-value<0.05); C) US (n=177) and non-US (n=167) practitioners answered the question “What is the best endovascular therapy for delayed cerebral ischemia?” the most common response was

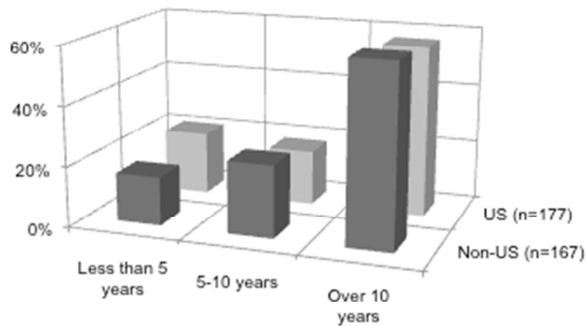
angioplasty (US 61%; Non US 51%), other choices included milrinone (US 1%; non-US 2%), nicardipine (US 3%; non-US 0%), nimodipine (US 1%; non-US 20%), papaverine (US 1%; non-US 1%), verapamil (US 9%; non-US 3%) and other agents (US 7%; non-US 12%) including glyceryl trinitrate and combination pharmaceutical endovascular therapies.

Table 1. Respondents' countries of practice (n)

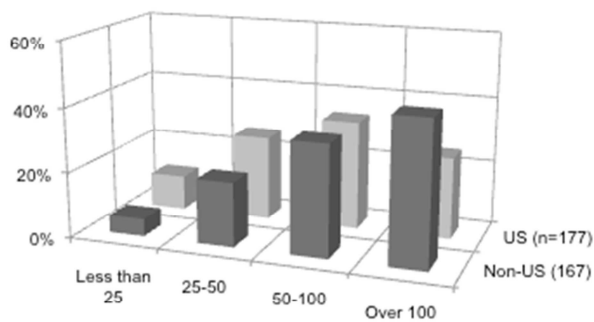
Australia & New Zealand	(27)	France	(9)	Jordan	(1)	South Africa	(2)
Austria	(11)	Germany	(9)	Latvia	(1)	Spain	(13)
Belgium	(3)	Hungary	(1)	Netherlands	(5)	Sweden	(5)
Canada	(1)	India	(1)	Pakistan	(1)	Switzerland	(9)
Croatia	(1)	Indonesia	(1)	Poland	(1)	Turkey	(3)
Denmark	(4)	Ireland	(1)	Portugal	(6)	UK	(32)
Egypt	(1)	Italy	(11)	Russia	(2)	USA	(177)
Finland	(1)	Japan	(1)	Serbia	(3)		

Figure 1

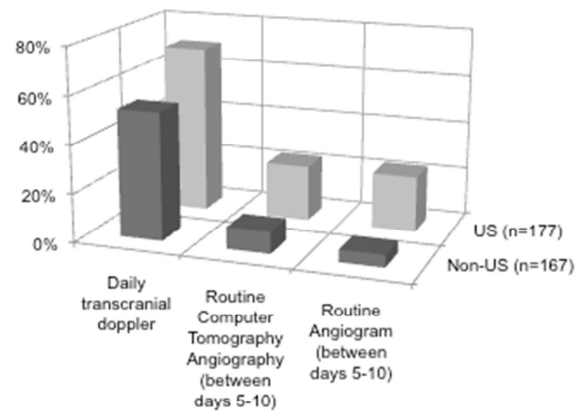
A. Years of experience managing aneurysmal subarachnoid hemorrhage amongst US and non-US responders



B. Case loads per year of aneurysmal subarachnoid hemorrhage amongst US and non-US responders



C. Use of screening techniques for delayed cerebral ischemia by US and non-US practitioners



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Figure 2

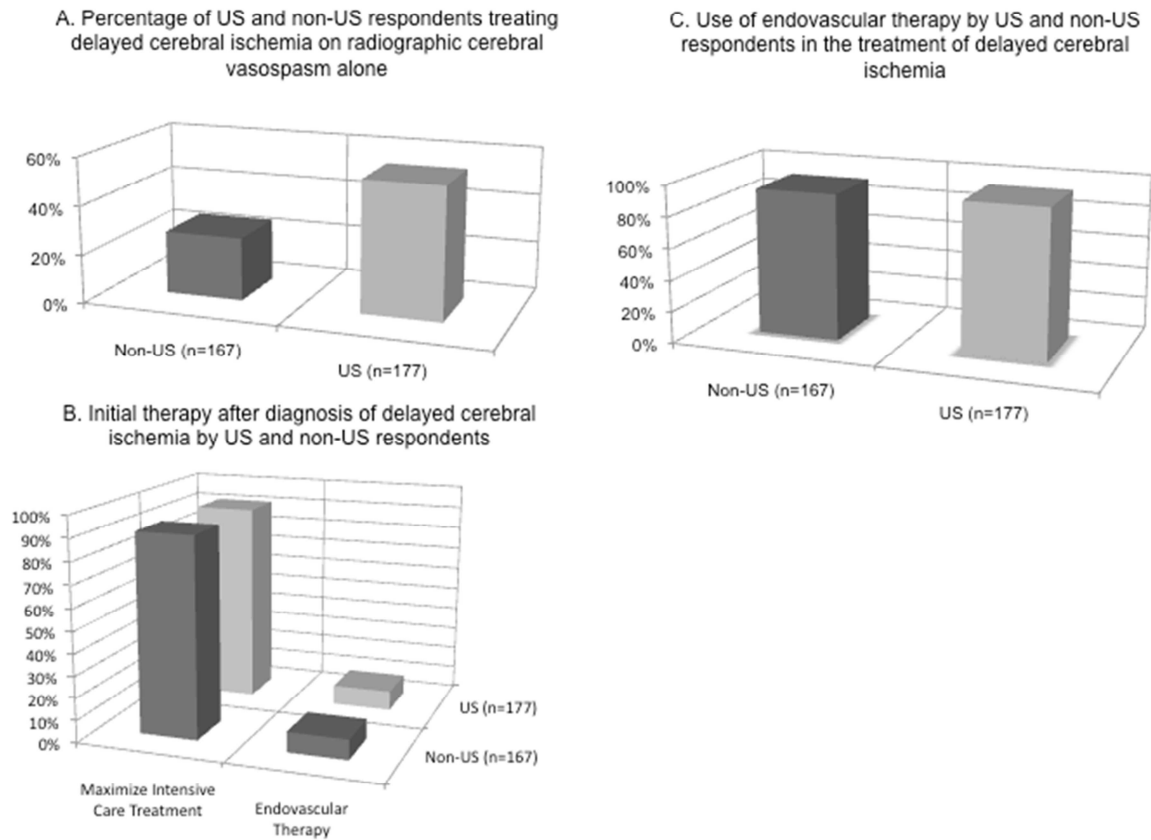
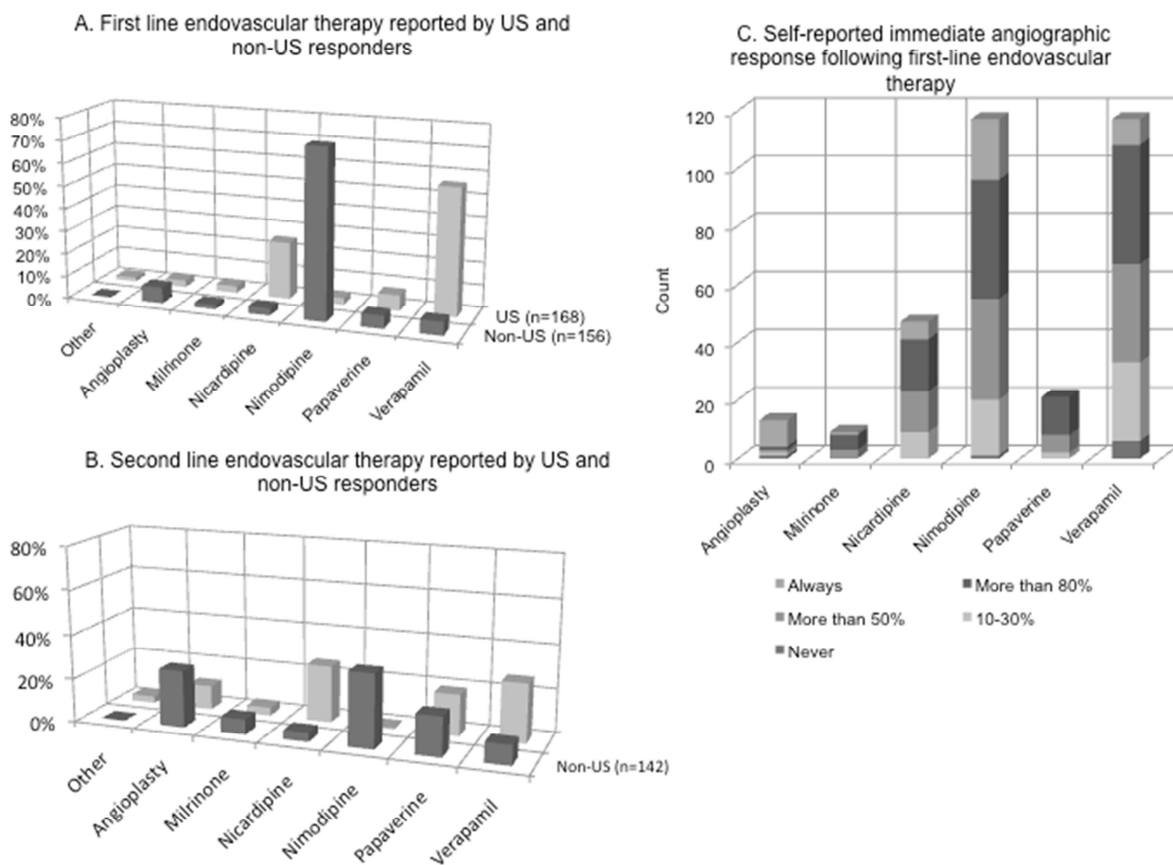


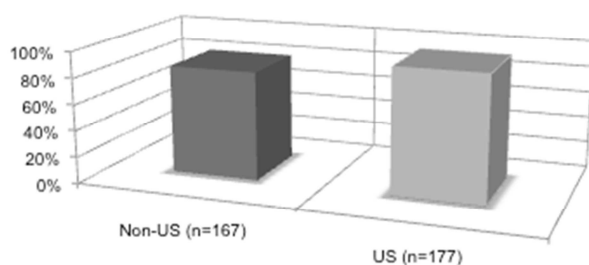
Figure 3



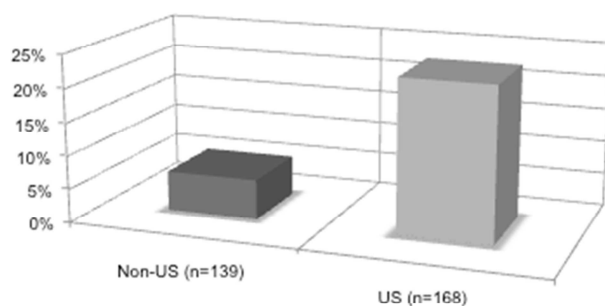
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Figure 4

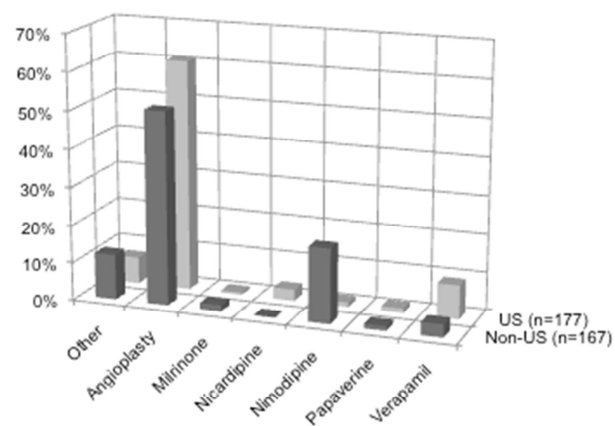
A. Use of angioplasty by US and non-US practitioners in the treatment of delayed cerebral ischemia



B. US and non-US responders using angioplasty for distal vasospasm



C. "What is the best endovascular treatment for delayed cerebral ischemia?": Answers from US and non-US respondents



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Highlights

- 344 clinicians from 32 countries reported current practices in the management of cerebral vasospasm
- Transcranial doppler was the screening method of choice to detect cerebral vasospasm
- The choice of first and second-line intra-arterial agents differ significantly between non-US and US respondents
- Most US and non-US clinicians reported angioplasty as the best treatment for cerebral vasospasm

Abbreviations

AANS/CNS	American Association of Neurological Surgeons/Congress of Neurological Surgeons
ANZINC	Australia and New Zealand Interventional Neuroradiology Collaborative
BSNR	British Society of Neuroradiology
CTA	Computer tomography angiography
CTP	Computer tomography perfusion
DCI	Delayed cerebral ischemia
DSA	Digital subtraction angiography
EEG	Electroencephalography
ESNR	European Society of Neuroradiology
MRA	Magnetic resonance angiography
MRS	Magnetic resonance spectroscopy
SAH	Subarachnoid hemorrhage
TCD	Transcranial doppler
UK	United Kingdom
US	United States of America

Conflict of interest declaration

We wish to draw the attention of the Editor to the following facts, which may be considered as potential conflicts of interest and to significant financial contributions to this work.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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Supplemental material 1. The 13-item questionnaire regarding the management of cerebral vasospasm and delayed cerebral ischemia

- 1 How long have you been in practice? Please select:
- A) <5 y B) 5-10y C) >10y
- 2 What is your volume of aneurysmal subarachnoid hemorrhage? Please select:
- A) <25 patients/y B) 25-50 C) 50-100 D) >100
 patients/y patients/y patients/y
- 3 How do you/your team screen for cerebral vasospasm? Please select:
- A) Daily B) Routine C) Routine D) Other
transcranial computer angiogram *Please*
Doppler tomography (between days *specify*
angiography 5-10)
(between days 5-
10)
- 4 When do you institute treatment for cerebral vasospasm? Please select:
- A) Radiographic findings of B) Endovascular treatment
vasospasm
- 5 What is your initial treatment for symptomatic cerebral vasospasm?
Please select:
- A) Maximize NICU management B) Endovascular treatment
- 6 If aggressive NICU management does not alleviate symptoms do
you/your team use endovascular methods to treat cerebral vasospasm?
Please select:
- A) Yes B) No

*Please skip remainder of
questions*

7 What is your first-line endovascular therapy to treat cerebral vasospasm?

Please select:

A) Verapamil B) Milrinone C) Nicardipin D) Papaverin E) Other

e e *Please
specify*

8 How often would you estimate that you see an immediate angiographic change after administration of your first-line endovascular agent? Please select:

A) Never B) <30% C) 50% D) 80% E)
Always

9 What is your second-line endovascular intra-arterial agent? Please select:

A) Verapamil B) Milrinone C) Nicardipin D) Papaverin E) Other

e e *Please
specify*

10 Do you/your team use angioplasty for cerebral vasospasm? Please select:

A) Yes B) No

If No, skip next question

11 Angioplasty is utilized for (select as many as apply)

A) Proximal Vasospasm B) Distal Vasospasm C) Never

(A2, M2, P2 etc)

12 The most effective endovascular treatment for cerebral vasospasm in my

practice is ...

Enter answer here

13 In your experience, how effective is endovascular treatment for cerebral vasospasm? Please select:

A) <10%

B) <50%

C) >50%

D) >80%