




Management and Outcomes of Delayed Cerebral Ischemia Associated with Vasospasm Post Nontraumatic Subarachnoid Hemorrhage: A Retrospective Cohort Study in the National Neurosurgical Center in Ireland

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J Neuroanaesthesiol Crit Care

Abstract

Background Delayed cerebral ischemia (DCI) is the leading cause of adverse outcome in patients who survive the initial phase of subarachnoid hemorrhage (SAH). While guidelines recommend induced hypertension as a first-line treatment for DCI, there is no high-level evidence confirming outcome benefit.

Methods Patients admitted with nontraumatic SAH over 3 years period were identified. Demographics, clinical/radiological presentation, aneurysm repair method, and Glasgow outcome score (GOS) 3 months postdischarge were recorded. A subgroup of patients who suffered clinically significant vasospasm were identified, and their hypertensive therapy and outcomes were examined.

Results A total of 532 patients were admitted with SAH; 68 developed vasospasm. The vasospasm subgroup was divided based on vasopressor treatment—norepinephrine alone ($n = 27$) versus norepinephrine plus vasopressin ($n = 35$). No correlation was found between percentage of days that mean arterial pressure (MAP) targets were met and GOS outcome. Patients treated with both agents had worse GOS outcomes at than those treated with norepinephrine alone.

Conclusion In our study, 12.8% of patients SAH developed vasospasm. Twenty-seven patients were treated with norepinephrine alone and 35 were treated with norepinephrine plus vasopressin to achieve augmented MAP targets. There was no correlation between percentage of days that MAP targets were met and improved patient outcome. The 68 patients stayed a total of 783 days in ICU, with a mean length of stay of 11.5 days. Patients who required dual therapy to achieve MAP targets had significantly worse neurological outcomes.

Keywords

- ▶ subarachnoid hemorrhage
- ▶ delayed cerebral ischemia
- ▶ cerebral vasospasm
- ▶ intracranial
- ▶ aneurysm
- ▶ hypertensive therapy

DOI <https://doi.org/10.1055/s-0044-1787880>.
ISSN 2348-0548.

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Introduction

Delayed cerebral ischemia (DCI) is the leading cause of poor outcome and death in patients who survive the initial phase of subarachnoid hemorrhage (SAH).¹ Approximately 30% of patients who suffer nontraumatic SAH develop DCI and/or infarction assumed to be primarily related to cerebral vasospasm.² Current guidelines recommend euvolemic hypertension as the mainstay of treatment for DCI.³ Vasopressors are routinely used to induce hypertension, sustain cerebral pressure gradients, and restore cerebral perfusion.⁴ While the guidelines do recommend induced hypertension, the evidence for this is questionable, with no randomized controlled trials of the approach confirming outcome benefit.⁵ Several different vasopressor agents are used to induce hypertension including phenylephrine, norepinephrine, and vasopressin, among others. There is not enough evidence in the literature to allow for a recommendation of the most suitable vasopressor or the dosing and titration of vasopressors for DCI.⁵

Our objectives in this study were to examine all patients admitted to the national neurosurgical center in Ireland with nontraumatic SAH over a 3-year period, assessing rates of vasospasm/DCI, choice of hypertensive therapy, length of intensive care unit (ICU) stay (LOS), and overall morbidity and mortality at 3 months postdischarge from hospital.

Materials and Methods

This study was performed in Beaumont Hospital, the national neurosurgical center in Ireland and was approved by the audit committee (CA753). All patients admitted to the hospital with nontraumatic SAH in the 3-year period from February 2016 to February 2019 were identified from the SAH database. Data extracted included: age at admission; sex; presence of risk factors for SAH (hypertension, ischemic heart disease, and smoking history); clinical scoring by Glasgow coma scale (GCS) and World Federation of Neurosurgical Societies (WFNS) grade at presentation; radiological scoring by Fisher grade; method of aneurysm treatment—endovascular occlusion or surgical clipping; occurrence of vasospasm; and Glasgow outcome score (GOS) at 3 months postdischarge from hospital. Regarding WFNS scoring and Fisher grading, the patients were examined as a dichotomy between low-grade and high-grade SAH presentation—WFNS grades 1 to 3 are considered low grade and 4 and 5 considered high grade; Fisher grades 1 and 2 as low grade and 3 and 4 as high grade.^{6,7} All patients admitted to the hospital with nontraumatic SAH were treated with calcium channel blockade in the form of nimodipine.

A subgroup of patients who had “vasospasm” recorded as part of their admission were identified by searching the neurosurgical and ICU databases. Patients were categorized as having clinically significant vasospasm and included in this subgroup if they met all three of the following criteria: (1) focal neurological deficit or a drop of two points in their GCS score; (2) radiological evidence of vasoconstriction of intracranial vessels on computed tomography (CT) angiogram or digital subtraction angiography (DSA); and (3) neurological deterior-

ation mandating ICU admission. Patients were only included in this subgroup if they required ICU admission as a result of a neurological deterioration secondary to vasospasm; patients whose reason for admission to ICU was not neurological deterioration secondary to vasospasm were not included in the cohort. The ICU records of the patients in this subgroup were then further analyzed, using the IntelliSpace Critical Care and Anesthesia Information System, Philips (► Fig. 1).

In our institution, mean arterial pressure (MAP) targets for hypertensive therapy are set by the attending neurosurgical consultant. The patients were reviewed each day by the neurosurgical consultant, who set MAP targets for each patient based on their clinical neurological status and their MAP at the time of review. Subsequent adjustments in MAP targets were again made by the neurosurgical consultant based on the neurological status of each patient on daily review.

Norepinephrine is routinely used as a first-line agent, with vasopressin used in addition to norepinephrine as a second-line treatment if MAP targets are not being met. Patients in this study were categorized into two groups—those treated with norepinephrine alone versus those treated with both norepinephrine and vasopressin. The mean rate of norepinephrine ($\mu\text{g}/\text{kg}/\text{min}$) and vasopressin (IU/min) was recorded for each day and a mean rate was then calculated over the length of the patient’s hypertensive therapy. The number of days for which each patient had MAP targets set by the attending physician, the value of these MAP targets, and the number of days for which the targets were achieved were recorded. A MAP target was considered achieved for a given day if the MAP was equal to or above the MAP target for more than 50% of the readings that day. A mean daily fluid balance was calculated. All complications noted in the patient record, including hyponatremia ($\text{Na} < 133$), and incidences of major morbidity, including myocardial infarction, tachyarrhythmias, and bowel ischemia were recorded. LOS of each patient was noted.

Data were analyzed using the chi-square or Fisher’s exact test for categorical variables and the independent sample *t*-test or Mann–Whitney’s *U* test for continuous variables, as appropriate. The association between percentage of days that MAP target was achieved and GOS scores at 3 months was examined using the Spearman’s rank order correlation. All data analysis was performed using IBM SPSS v26 software. A *p*-value < 0.05 was considered statistically significant.

Results

Of 532 patients who were admitted with nontraumatic SAH, 68 (12.8%) developed vasospasm-associated DCI requiring ICU admission; 103 patients had no underlying aneurysm identified on DSA. Only one of these patients without an identified aneurysm went on to develop vasospasm/DCI requiring hypertensive therapy. There was no association between treatment type of underlying aneurysm (endovascular or surgical) and the development of clinically significant vasospasm ($p = 0.441$). Of the 68 patients with clinically significant angiographic vasospasm, 9 patients (13.2%) underwent an angioplasty procedure (either with intra-arterial

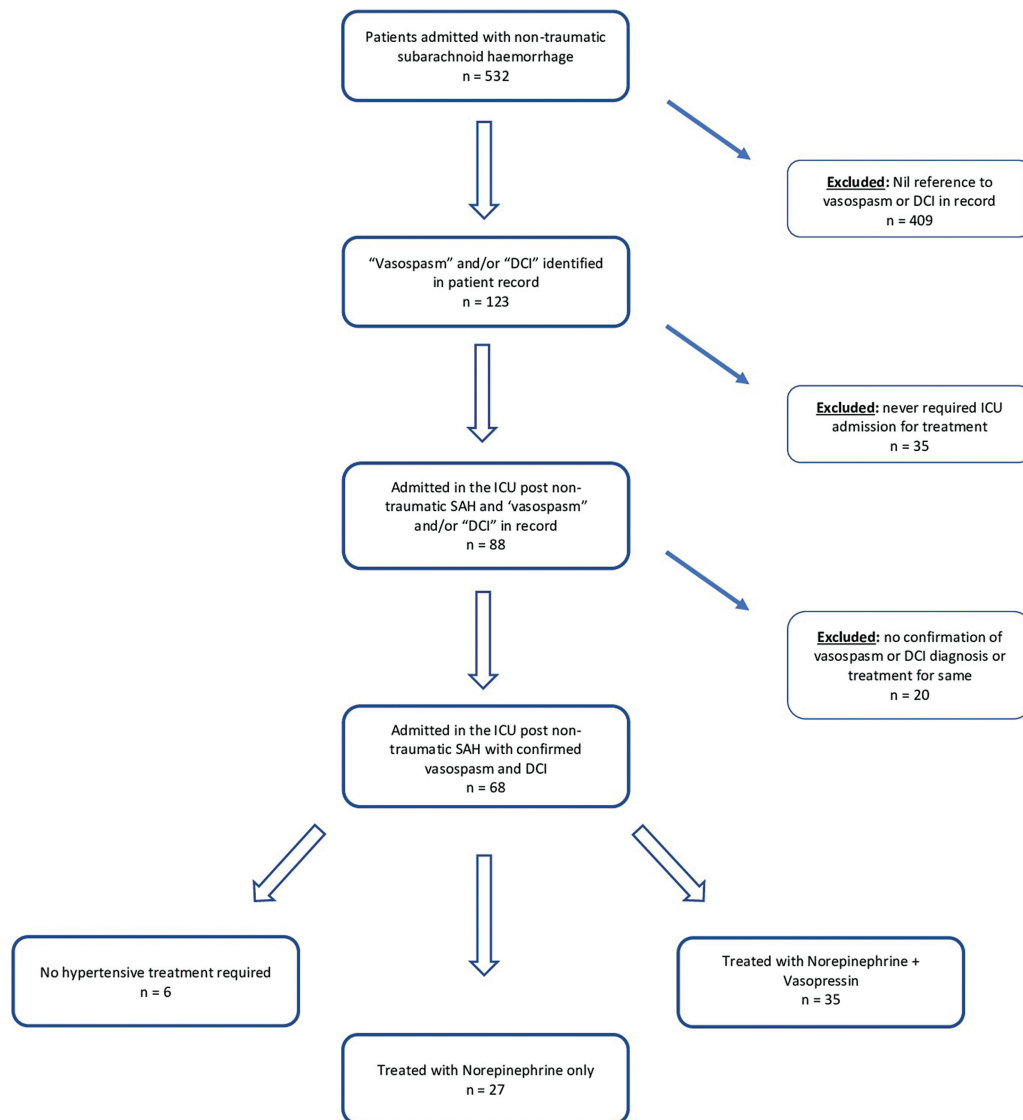


Fig. 1 Patient inclusion/exclusion criteria followed by breakdown of hypertensive therapy in final cohort who developed vasospasm. DCI, delayed cerebral ischemia; ICU, intensive care unit; SAH, subarachnoid hemorrhage.

vasodilators or balloon dilatation). There was an association between female sex (chi-square test, $p = 0.010$), higher WFNS grades (Mann–Whitney’s U test, $p = 0.004$), and higher radiological grading (Mann–Whitney’s U test, $p < 0.001$) and the development of vasospasm-associated DCI (► **Table 1**).

Three-month outcome data showed that those patients who suffered vasospasm-associated DCI had significantly worse outcomes than those who did not (Mann–Whitney’s U test, $p < 0.001$). At 3 months postadmission, 255/464 (55%) of patients who did not suffer vasospasm-associated DCI achieved a GOS of 5, indicating a good recovery. Ninety-three (20%) were disabled but independent (grade 4), 59 (12.7%) were disabled and dependent (grade 3), 3 (0.6%) were unresponsive (grade 2), and the remaining 54 (11.6%) did not survive (grade 1). Of those who developed vasospasm-associated DCI, 22/68 (35.5%) achieved a GOS of 5, while 18 (29%) were GOS 4, 16 (25.8%) were GOS 3, and the remaining 6 patients (9.7%) did not survive.

The 68 patients who required treatment in the ICU for vasospasm-associated DCI stayed a combined 783 days in the ICU, with a mean LOS of 11.5 days (range 1–38 days). Twenty-seven patients received norepinephrine alone and 35 patients received norepinephrine plus vasopressin (► **Table 2**). Six patients were excluded from the further analysis as they maintained their MAP targets and/or improved clinically without the need for hemodynamic augmentation. The mean ICU LOS for the group that did not require vasopressor therapy was 5 days (range 1–16 days).

There was no significant difference in mean age at presentation between the two vasopressor groups (t -test, $p = 0.263$), and there was no association between sex and the requirement for a second vasopressor agent (chi-square test, $p = 0.502$). Within the cohort who developed vasospasm-associated DCI, there was an association between high-grade clinical scores but not radiological scores of SAH severity at presentation and the requirement for higher doses of norepinephrine and the

Table 1 Analysis of baseline demographics, aneurysm location, treatment type, clinical/radiological presentation, and outcome data of patients who developed vasospasm versus those who did not

	Developed DCI	Did not develop DCI	p-Value
Number of patients	68 (12.8%)	464 (87.2%)	
Mean age	55.4	55.4	0.989
Female gender	52/68 (76.5%)	280/464 (60.3%)	0.010 [†]
HTN	27/68 (39.7%)	153/459 (33.3%) HTN history unknown: 5 patients	0.301
IHD	2/68 (2.9%)	20/459 (4.4%) IHD history unknown: 5 patients	0.586
DSA negative	1/68	102/464	0.000 [†]
Aneurysm location	Anterior circulation = 65 Vertebrobasilar = 2 DSA negative = 1	Anterior circulation = 308 Vertebrobasilar = 44 DSA negative = 102 Unknown location = 10	
Treatment type	Endovascular 55/67 Surgical 12/67	Endovascular 289/337 Surgical 48/337	0.441
WFNS grade	1 = 25 (36.8%) 2 = 19 (27.9%) 3 = 5 (7.4%) 4 = 14 (20.6%) 5 = 5 (7.4%)	1 = 273 (58.8%) 2 = 79 (17%) 3 = 13 (2.8%) 4 = 57 (12.3%) 5 = 42 (9.1%)	0.004 [†]
Fisher grade	1 = 2 (2.9%) 2 = 4 (5.9%) 3 = 8 (11.8%) 4 = 54 (79.4%)	1 = 38 (8.2%) 2 = 72 (15.5%) 3 = 96 (20.7%) 4 = 258 (55.6%)	0.000 [†]
GOS at 3 mo	5 = 22 (35.5%) 4 = 18 (29%) 3 = 16 (25.8%) 2 = 0 1 = 6 (9.7%)	5 = 255 (55%) 4 = 93 (20%) 3 = 59 (12.7%) 2 = 3 (0.6%) 1 = 54 (11.6%)	0.000 [†]

Abbreviations: DCI, delayed cerebral ischemia; DSA, digital subtraction angiography; HTN, hypertension; IHD, ischemic heart disease; GOS, Glasgow outcome score; WFNS, World Federation of Neurological Societies.

addition of vasopressin (Mann–Whitney's *U* test, $p = 0.03$ and $p = 0.737$, respectively).

There was no statistical difference in the daily MAP targets set in each group, nor was there a difference in the percentage of days in which these MAP targets were met. In the norepinephrine only group, the MAP targets set were 102.6 ± 12.4 mm Hg (mean \pm standard deviation [SD]) versus 104.3 ± 12.5 mm Hg (mean \pm SD) in the group treated with both norepinephrine and vasopressin (*T* test, $p = 0.129$). The number of overall days in which these MAP targets were met was 167/190 (87.8%) in the norepinephrine alone group versus 352/389 (90.4%) in the norepinephrine plus vasopressin group (chi-square test, $p = 0.336$). At 3 months postdischarge from hospital, the group that required a second vasopressor agent had worse GOS outcomes than the group that required norepinephrine only (Mann–Whitney's *U* test, $p = 0.043$) (– **Table 2**).

Patients who received norepinephrine plus vasopressin were found to have a significantly higher daily positive fluid balance in days 1 to 5 of their hypertensive therapy (mean fluid balance/day of +380.6 mL) when compared with those who received norepinephrine alone (mean +99.7 mL) ($p = 0.038$). A significant proportion of the patients treated with norepi-

nephine plus vasopressin developed hyponatremia ($\text{Na} < 133$ mmol/L) compared with those treated with norepinephrine only; 28/33 (84.8%) patients who were treated with norepinephrine plus vasopressin had a drop in their sodium to below 133 mmol/L versus 8/24 (33.3%) of those treated with norepinephrine alone ($p < 0.01$). Two patients in the norepinephrine plus vasopressin group and three in the norepinephrine only group were excluded from this calculation because they were hyponatremic prior to the induction of hypertensive therapy.

There was no correlation found between the percentage of days patients achieved their MAP targets and GOS scores at 3 months postdischarge ($r_s = 0.131$, $p = 0.314$). There were no incidences of sustained tachyarrhythmias, myocardial infarction, or bowel ischemia recorded for the patients receiving hypertensive therapy for the duration of their treatment. One patient in the norepinephrine plus vasopressin group developed a lower respiratory tract infection.

Discussion

In keeping with prior studies, our data highlight the markedly inferior neurological outcomes experienced by patients who develop vasospasm-associated DCI following

Table 2 Baseline demographics, clinical/radiological presentation, MAP target data, management, and outcome data of patients who developed vasospasm divided by type of hypertensive therapy received

	Norepinephrine only	Norepinephrine and Vasopressin	p-Value
No. of patients	27	35	
Mean age	57.3	54.4	0.263
Female gender	22/27	26/35	0.502
WFNS grade	1 = 11 (40.7%) 2 = 8 (29.6%) 3 = 4 (14.8%) 4 = 3 (11.1%) 5 = 1 (3.7%)	1 = 12 (34.3%) 2 = 8 (22.9%) 3 = 1 (2.9%) 4 = 10 (28.6%) 5 = 4 (11.4%)	0.206
WFNS—low grade vs. high grade	Low grade = 23/27 High grade = 4/27	Low grade = 21/35 High grade = 14/35	0.030*
Fisher grade	1 = 2 (7.4%) 2 = 1 (3.7%) 3 = 4 (14.8%) 4 = 20 (74.1%)	1 = 0 2 = 3 (8.6%) 3 = 3 (8.6%) 4 = 29 (82.9%)	0.390
Fisher grade—low grade vs. high grade	Low grade = 3/27 High grade = 24/27	Low grade = 3/35 High grade = 32/35	0.737
Mean hours from ictus to aneurysm secured	78.22	83.4	0.754
Daily MAP target, mm Hg, mean ± SD	102.6 ± 12.4	104.3 ± 12.5	0.129
Norepinephrine infusion rate—daily, µg/kg/min, mean ± SD	0.129 ± 0.098	0.218 ± 0.158	0.000*
Vasopressin infusion rate—daily, units/min, mean		0.02	
% days that MAP target achieved	87.8% 167/190	90.4% 352/389	0.336
Mean daily fluid balance (mL) over days 1–5	99.7	380.6	0.038*
Angioplasty procedures	2/27	6/35	0.257
GOS at 3 mo	5 = 13 (48.1%) 4 = 8 (29.6%) 3 = 4 (14.8%) 2 = 0 1 = 2 (7.4%)	5 = 9 (25.7%) 4 = 10 (28.6%) 3 = 12 (34.3%) 2 = 0 1 = 4 (11.4%)	0.043*

Abbreviations: GOS, Glasgow outcome score; MAP, mean arterial pressure; WFNS, World Federation of Neurological Societies.

nontraumatic SAH, with significantly worse GOS scores 3 months posthospital discharge, when compared with patients without DCI. Importantly, and consistent with prior reports, we identified several risk factors for vasospasm-associated DCI within our cohort; both female sex and a higher grade of SAH at presentation (clinical and radiological) were significantly associated with the subsequent development of vasospasm-associated DCI.

Despite the clear morbidity of vasospasm-associated DCI, the evidence supporting the use of induced hypertension as a therapeutic approach comes primarily from case series and observational studies.^{8,9} The premature termination of a multicenter randomized controlled trial (HIMALAIA) examining the efficacy of induced hypertension highlights the significant challenges in obtaining high-level evidence for this treatment; the trial was stopped prematurely due to poor recruitment and a signal of increased serious adverse events within the induced hypertension subgroup.¹⁰

Our data highlight that escalating doses of norepinephrine and the addition of vasopressin appears to be effective in

improving MAP; both patients on combination and single agent therapy showed high rates of achievement of daily MAP targets (~90% in both groups). However, achieving MAP targets did not necessarily translate into positive clinical outcome; we found no association between the percentage of days that MAP targets were met and neurological outcome. Importantly, patients who required dual therapy to achieve target MAP had significantly worse neurological outcomes at 3 months postdischarge. This adverse outcome is likely partially due to higher WFNS grade at presentation, but whether it may be further compounded by the adverse effects of hypertensive therapy is unclear. Importantly, patients receiving dual therapy had evidence of potential side effects related to hypertensive therapy in the short term, with significantly higher rates of hyponatremia and fluid retention relative to patients on single agent therapy.

Both human and animal studies offer a mechanistic basis for concern regarding adverse effects of induced hypertensive therapy. Animal models have demonstrated that norepinephrine directly results in cerebral vasoconstriction.^{11,12} In

healthy volunteers, high-dose norepinephrine infusions have been shown to increase cerebrovascular resistance.¹³ Decreased cerebral oxygenation has also been reported in healthy controls at norepinephrine infusion rates above 0.1 µg/kg/min, doses consistent with those seen in our cohort.¹⁴ The use of vasopressor infusions following nontraumatic SAH resulted in decreased cerebral regional oxygenation in one study, despite increases in systemic pressure,¹⁵ highlighting a disconnect between MAP and cerebral perfusion. There are also case reports illustrating a potential worsening of vasospasm after norepinephrine therapy is administered.¹⁶

Arginine vasopressin is a nonapeptide which acts via V1 receptors in vascular smooth muscle to cause intense vasoconstriction resulting in increases in systemic pressure.¹⁷ Similar to norepinephrine, the effect of vasopressin on the cerebral vasculature is unclear and to date, there have been no controlled studies demonstrating an outcome benefit from vasopressin in DCI treatment. Results from animal studies have implicated endogenous arginine vasopressin in the development of cerebral vasospasm post-SAH.^{18,19} Furthermore, it has been proposed that antagonism of vasopressin V1a receptors can significantly reduce brain edema formation postischemic stroke and traumatic brain injury.²⁰ Indeed, in a rat model of SAH, *antagonism* of the V1a receptor led to decreased initial hemorrhage, rebleeding rates, and improved neurological outcomes.²¹

Cumulatively, therefore, there remains concern regarding the efficacy and safety of hypertensive therapy with norepinephrine and vasopressin in patients who suffer vasospasm-associated DCI post-SAH. There is a need for further studies to investigate the optimum vasopressor agent and dosing regimen, while research into new treatment options would also be welcome. Recent evidence, though limited, has suggested that the phosphodiesterase inhibitor milrinone, for example, may be a safe and effective treatment for DCI and may be associated with improved long-term functional outcomes.²²

Our study has several important limitations which should be addressed. It is a retrospective single-center study of a small sample size. As such, it is not the appropriate study design to make definitive comments on the impact of hypertensive therapy on outcome after DCI in nontraumatic SAH. As stated earlier, the difference in outcome between the two vasopressor groups can be explained, at least in part, by the severity of grades of SAH at presentation. While every effort was made to record all complications suffered by the patients during their ICU stay, complications were not accounted for in the statistical analysis. There may also have been adverse events which were not recorded and therefore not included in the study. Complications such as the development of sepsis can have a large effect on the vasopressor requirements and outcomes of critically ill patients. Similarly, we do not have definitive data detailing whether any patients developed new infarcts on CT scan after treatment, which could also have an independent adverse effect on outcome. We also do not have definitive data (e.g., echocardiography) detailing the cardiac function of patients during their hypertensive therapy, another variable which could potentially affect outcome. Finally, though fluid retention was a statisti-

cally significant complication of those patients treated with both norepinephrine and vasopressin, it is possible that this complication did not translate into having a clinically significant adverse effect on these patients.

Conclusion

Our data highlight the large impact which the development of DCI/vasospasm continues to have on the outcomes of patients who have suffered nontraumatic SAH. The lack of high-level evidence supporting outcome benefit from induced hypertensive therapy in the treatment of DCI associated with vasospasm remains troubling. While escalating therapy with higher dose norepinephrine in addition to vasopressin allowed MAP targets to be achieved, there was no correlation between the percentage of days that MAP targets were met and neurological outcome. Although caveated by the higher clinical and radiological scores prior to treatment escalation, there was a potential association between the use of higher dose norepinephrine in addition to vasopressin and worse neurological outcome at 3 months postdischarge. Our data highlight the urgent need for further studies into the efficacy and risks of induced hypertensive therapy for DCI post-SAH, while there is also a need for investigation of newer treatment options for the strategy.

Conflict of Interest

None declared.

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