Induced Hypertension for Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

A Randomized Clinical Trial

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Background and Purpose—Induced hypertension is widely used to treat delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage, but a literature review shows that its presumed effectiveness is based on uncontrolled case-series only. We here report clinical outcome of aneurysmal subarachnoid hemorrhage patients with DCI included in a randomized trial on the effectiveness of induced hypertension.

Methods—Aneurysmal subarachnoid hemorrhage patients with clinical symptoms of DCI were randomized to induced hypertension or no induced hypertension. Risk ratios for poor outcome (modified Rankin Scale score >3) at 3 months, with 95% confidence intervals, were calculated and adjusted for age, clinical condition at admission and at time of DCI, and amount of blood on initial computed tomographic scan with Poisson regression analysis.

Results—The trial aiming to include 240 patients was ended, based on lack of effect on cerebral perfusion and slow recruitment, when 21 patients had been randomized to induced hypertension, and 20 patients to no hypertension. With induced hypertension, the adjusted risk ratio for poor outcome was 1.0 (95% confidence interval, 0.6–1.8) and the risk ratio for serious adverse events 2.1 (95% confidence interval, 0.9–5.0).

Conclusions—Before this trial, the effectiveness of induced hypertension for DCI in aneurysmal subarachnoid hemorrhage patients was unknown because current literature consists only of uncontrolled case series. The results from our premature halted trial do not add any evidence to support induced hypertension and show that this treatment can lead to serious adverse events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01613235.

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Key Words: aneurysmal subarachnoid hemorrhage ■ delayed cerebral ischemia ■ induced hypertension ■ randomized controlled trial

Delayed cerebral ischemia (DCI) is a major contributor to poor outcome after aneurysmal subarachnoid hemorrhage (aSAH).[1] For 3 decades, induced hypertension, used alone or in combination with hemodilution and hypervolemia, the so-called triple-H therapy, has been used with the aim of restoring impaired cerebral perfusion,[2] and thereby improving outcome. However, this treatment is not supported by any controlled study and carries a risk of serious complications. In a systematic review of the literature, of the components of this triple-H therapy, only induced hypertension seemed useful in actually increasing cerebral blood flow.[3] The aim of this randomized trial was to assess the effectiveness of induced hypertension on clinical outcome in patients with DCI after aSAH.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

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Study Design and Patients

From 2009 to 2015, we performed a multicenter, single-blinded, randomized trial with masked outcome assessment in 4 hospitals in the Netherlands to assess the effects of induced hypertension on cerebral perfusion and clinical outcome in aSAH patients with DCI. The study was approved by the medical ethics committee (protocol number METC 2010_157) and all participating hospitals.

The trial design including in- and exclusion criteria for participation was published previously.[4] In short, informed consent was obtained as soon as possible after admission. In case of a depressed level of consciousness, the patient's legal representative was asked for informed consent. Eligible patients in whom informed consent was obtained and in whom the symptomatic aneurysm was occluded were randomized at the time of development of DCI, defined as a decrease of at least 1 point on the Glasgow Coma Scale sum score or development of new focal neurological deficits lasting at least 1 hour, or both, with exclusion of other prespecified explanations for clinical deterioration. To exclude these other options, we routinely performed a computed tomographic (CT) scan of the brain to rule out hydrocephalus and sampled blood to determine leucocytes count and serum CRP (C-reactive protein), sodium, creatinine, urea, and glucose to exclude a metabolic encephalopathy. In case of any suspicion, an electroencephalogram was performed to rule out seizures.

We further excluded patients with a spontaneous mean arterial pressure (MAP) >120 mm Hg at time of randomization and patients with contraindications for induced hypertension according to the treating physician. Randomization was initially performed using sealed opaque envelopes but later changed to Web-based randomization with stratification for treatment center with maximum random block size of 8.[4]

Interventions

Patients were randomized to induced hypertension or no hypertension (no hypertension group). Hypertension needed to be started within 3 hours after the start of clinical symptoms of DCI. Hypertension was induced with fluids and norepinephrine over a central venous line placed for this purpose in the intensive care unit (ICU) according to the local protocol of the participating center. The treatment was continued until improvement of neurological deficits, occurrence of a complication, a maximum MAP of 130 mm Hg, or a systolic blood pressure of 230 mm Hg. Clinical improvement within 24 hours was judged by the unblinded treating clinician. In case of clinical improvement, norepinephrine was continued for at least 48 hours and then slowly tapered. In case of recurrence of symptoms during tapering, norepinephrine was restarted and tapering was attempted 24 hours later. In the absence of clinical improvement within 24 hours, norepinephrine was tapered. In the no hypertension group, hypertension was not induced, but a minimal MAP of 80 mm Hg was maintained with fluids and, when necessary, with vasopressors. In the latter case, a central venous line was placed, but otherwise, no central venous lines were used in the no hypertension group. Patients in the hypertension group were managed at the ICU and patients in the no hypertension group could be managed either at a neuro-medium care unit or ICU depending on blood pressure and level of consciousness. In case of a second episode of DCI, treatment was performed according to the initial randomization. Hourly, nurse-validated invasive measures of MAP were obtained for analyses. In patients in the no hypertension group who remained at the neuro-medium care unit, MAP was obtained noninvasively at least 4 hourly. All patients were treated with oral nimodipine and fluid administration aimed at normovolemia. In 3 of the 4 participating centers, a substudy was performed to assess the efficacy of induced hypertension in augmenting cerebral blood flow by means of cerebral perfusion CT scanning.[5] In these patients, follow-up CT perfusion was obtained 24 to 36 hours after randomization. In the fourth center, follow-up CT or magnetic resonance imaging was not routinely performed.

Outcome Measures

Outcome measures were obtained by research nurses blinded for treatment allocation. The primary outcome measure was poor outcome at 3 months (modified Rankin Scale >3).[6] Secondary outcome measures were cerebral perfusion assessed with CT perfusion (data published previously[5]), 30-day case-fatality, and, at 3 months after randomization: activities of daily living (Barthel Index[7]), quality of life (Stroke Specific Quality of Life Scale[8]), anxiety and depression (Hospital Anxiety and Depression Scale[9]), and cognitive functioning (Cognitive Failures Questionaire[10]). All serious adverse events (SAE's) were recorded during hospital admission by the principle investigator.[4] For the current study, an SAE was defined according to the definition made by the Central Committee on Research Involving Human Subjects (the Centrale Commissie Mensgebonden Onderzoek) at the time of drafting the study protocol, following the definition made by the European Commission. The Centrale Commissie Mensgebonden Onderzoek defines an SAE as follows: an SAE is any untoward medical occurrence in a patient or trial subject, which does not have a causal relationship with the treatment, and: (1) results in death; (2) is life threatening (at the time of the event); (3) requires prolongation of inpatients' hospitalization; (4) results in persistent or significant disability or incapacity; (5) is a new event of the trial likely to affect the safety of the subjects.[11–13] For the present study, SAEs were defined according to the definition above, within the timeframe of hospital admission. In case of death, the cause of death was determined by the principle investigator of each participating center. In case the cause of death was not immediately clear, the entire period of hospital admission was reviewed to establish the factors contributing to death.

Statistical Analysis

With an expected frequency of poor outcome of 42%, power of 80%, and significance level set at 0.05, we calculated that a sample of 120 patients per group would be needed to detect a relative risk of 0.60 for poor outcome associated with induced hypertension. MAP over time was compared between groups with a linear mixed model. We calculated risk ratio's with corresponding 95% confidence intervals (CI) for poor outcome and for occurrence of SAEs. In addition, we computed adjusted risk ratios for poor outcome, adjusted for age, clinical condition at admission, and at time of DCI based on the World Federation of Neurosurgical Societies scale[14] and amount of blood on initial CT scan using the Hijdra-score, with Poisson regression analysis. We primarily performed an intention-to-treat analysis and added an on-treatment sensitivity analysis. For the remaining secondary outcome measures, differences between groups were assessed with Mann–Whitney *U* tests.

Trial Organization

An independent data safety monitoring board (DSMB) was appointed for this study and consisted of a biostatistician, a neurologist-intensivist, and an internist-intensivist, none of whom were involved in the trial otherwise. The responsibility of the DSMB was to assess safety, continued scientific value, overall conduct of the trial, treatment harm and recruitment, with the aim of providing recommendations on (dis)continuation of the trial. Reports to the DSMB were provided by the study coordinator every 3 months or after every 5 randomized patients. The DSMB met at least every 6 months. A formal interim analysis was planned after 120 patients completed the trial. In 2014, an additional interim analysis was advised by the DSMB when recruitment was slow, after 24 patients completed the substudy on cerebral perfusion. The aim of this interim analysis was to calculate how much patients would be needed to find a statistically significant difference in cerebral perfusion and assess feasibility of continuation of the trial based on safety data of all included patients at that time.

Results

The trial was prematurely terminated based on advice of the Data Safety Monitoring Board because of lack of effect on overall cerebral perfusion[5] and slow recruitment resulting in the conclusion that it would be unfeasible to obtain sufficient numbers of included subjects within a reasonable time frame. At the time of termination of the trial, in total

an estimated 1627 patients had been screened for participation of whom 736 were eligible. In one of the participating centers, enrolling 5 patients in total, the documentation of the exact number of patients screened for participation was not structurally assessed at the beginning of the trial. This center stopped including patients after 2 years. Of all eligible patients (n=736), 248 gave informed consent, and of these, 41 developed DCI and could be randomized: 21 to induced hypertension and 20 to the no hypertension group (Table 1). In 1 patient, randomized to the hypertension group, treatment was not started because of the discovery of a previously unknown cardiomyopathy. Twenty-five of the 41 randomized patients also participated in the substudy on cerebral perfusion.[5]

The MAP over the first 24 hours was 11.1 mm Hg (95% CI, 7.1–15.1) higher in the hypertension group than in no hypertension group. The difference in MAP between the hypertension group and the no hypertension group over 72 hours was, on average, 5.7 mm Hg (95% CI, 4.2–8.5 mm Hg; Figure). In 5 of the 20 patients in the no hypertension group, norepinephrine was administered over a central venous line for several hours to prevent a MAP <80 mm Hg.

Poor outcome occurred in 12 of 21 (57%) patients in the hypertension group and in 8 of 20 (40%) patients in the no hypertension group. With induced hypertension, the risk ratio for poor outcome was 1.4 (95% CI, 0.7–2.7) and the adjusted risk ratio 1.0 (95% CI, 0.6–1.8). In the on-treatment analyses, the adjusted risk ratio for poor outcome associated with induced hypertension was 1.1 (95% CI, 0.6–1.9).

Eighteen patients showed clinical improvement within 24 hours (n=12, 57% in the hypertension group and n=6, 30% in the no hypertension group), defined as any improvement in Glasgow coma score or improvement of focal deficits, according to the treating clinician. Five of the 12 patients with initial improvement after induced hypertension had a poor outcome at 3 months, whereas 0 of the 6 patients with initial improvement without induced hypertension had a poor outcome at 3 months.

Secondary outcome measures are shown in Table 1. Sixteen SAE's occurred, 11 (52%) in the hypertension group versus 5 (25%) in the no hypertension group, risk ratio 2.1 (95% CI, 0.9–5.0).

Specification of the SAE's in the hypertension group versus the no hypertension group was as follows: death 6/4, pneumothorax 2/0, atrial fibrillation 1/0, myocardial infarction 2/0, ECG changes (diffuse negative ECG T-waves): 0/1. Specification of the deaths was as follows: 6 patients died in the hypertension group because of persistent poor neurological condition due to the aSAH and DCI (n=2), pneumosepsis superimposed on poor neurological condition (n=1), rebleeding from previously coiled symptomatic aneurysm, weeks after discharge (n=1), combination of poor neurological condition, acute coronary syndrome, pneumosepsis, and metabolic disturbances (n=1), and unexpected death of unknown cause 1 day before discharge from the hospital (n=1). Four patients died in the no hypertension group because of persistent poor neurological condition due to the aSAH and DCI (n=3) and pneumonia superimposed on poor neurological condition (n=1). In 1 patient in the hypertension group,

Table 1. Patient Characteristics and Outcome Measures per Group

	Induced Hypertension (n=21)	No Hypertension (n=20)	RR (95% CI)
Patient characteristics			
Age, mean (SD)	63 (12)	57 (10)	
Female (%)	15 (71)	16 (80)	
Medical history of hypertension (%)	5 (24)	4 (20)	
Admission-WFNS-score >3	12 (57)	8 (40)	
WFNS-score at DCI >3	13 (62)	11 (55)	
Anterior circulation aneurysm (%)	16 (76)	13 (65)	
Hijdra sum score >median of 28 (%)	13 (62)	7 (35)	
Clip/coil (%)	9(43)/12(57)	8(40)/12(60)	
Rebleeding (%)	1 (5)	2 (10)	
Days between aSAH and DCI, median (IQR)	6 (4–7)	8 (5–9.8)	
Time DCI to start of hypertension (h), median (IQR)	3.4 (3–5.4)	–	
Baseline MAP, mean (SD)	99 (13)	99 (11)	
Outcome measures			
Poor outcome at 3 mo, mRS >3 (%)	12 (57)	8 (40)	1.0* (0.6–1.8)
mRS (%) 0	0	2 (11)	
1	1 (5)	4 (21)	
2	6 (29)	3 (16)	
3	2 (10)	3 (16)	
4	3 (14)	3 (16)	
5	3 (14)	1 (5)	
6	6 (29)	4 (21)	
SAE's	11 (52)	5 (25)	2.1 (0.9–5.0)
ADL (Barthel Index[7]; median, IQR)†	20 (10–20)	20 (16–20)	
Quality of life (SSQoL[8]; median, IQR)†	47 (35–55)	49 (35–55)	
Anxiety and depression (HADS[9]; median, IQR)†	13 (3–13)	8 (4–11)	
Cognitive functioning (CFQ[10]; median, IQR)†	29 (16–54)	26 (15–33)	

ADL indicates activities of daily living; aSAH, aneurysmal subarachnoid hemorrhage; CFQ, Cognitive Failures Questionnaire; CI, confidence interval; CT, computed tomography; DCI, delayed cerebral ischemia; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; MAP, mean arterial pressure; mRS, modified Rankin Scale at 3 months; RR, risk ratio; SSQoL, Stroke Specific Quality of Life Scale; and WFNS, World Federation of Neurosurgical Societies.

*Adjusted for age, clinical condition at admission, clinical condition at time of DCI, and amount of blood on initial CT scan.

†Assessed in 9 patients in the hypertension group and 11 patients in the no hypertension group.

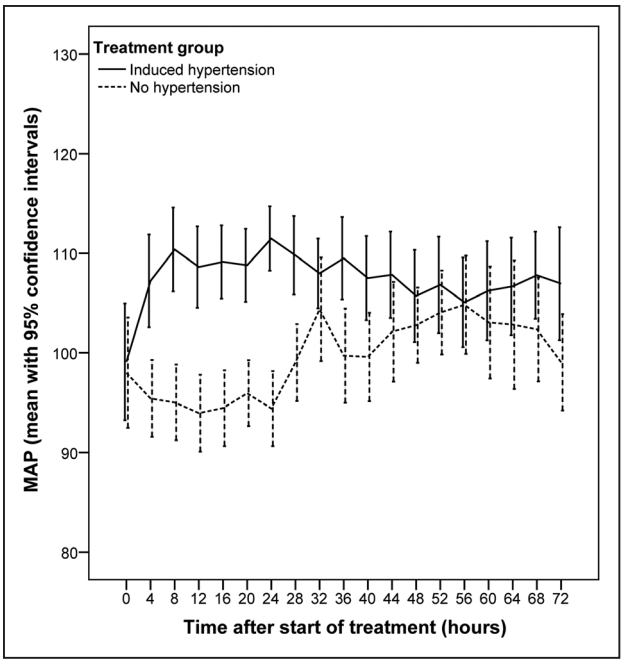

Figure. Mean arterial pressure (MAP) over time per group.

more than 1 SAE occurred. This patient developed 3 SAEs: a pneumothorax because of insertion of the central venous line necessary for the administration of norepinephrine, an acute coronary syndrome after initiation of induced hypertension for which induced hypertension was tapered, and death because of a combination of poor neurological condition, the acute coronary syndrome, pneumosepsis, and metabolic disturbances. All these events were judged as individual SAEs following the predefined definition for a SAE.

Discussion

In this randomized trial, induced hypertension effectively increased blood pressure. Because the study was stopped prematurely because of lack of efficacy on cerebral blood flow and slow recruitment, it remains underpowered and therefore does not provide any evidence to support induced hypertension in aSAH patients with DCI. Our study also shows that induced hypertension can lead to serious adverse events. The unblinded treating physicians had the impression that induced hypertension improved the symptoms associated with clinical DCI, but the trial showed that clinical improvement also occurs in the absence of induced hypertension.

To put our data in perspective with the current available literature, we performed an extensive literature search in the Entrez PubMed NIH and EMBASE online medical databases, and the central COCHRANE Controlled Trial Register (last search date August 31, 2017), using the search string outlined in Table 2. Reference lists were checked for completeness. We included only original reports, based on adult human subjects with proven aSAH. At least part of the study population had to be treated with induced hypertension with vasopressors as treatment for clinical signs of DCI. Only studies that reported on clinical response to the treatment or effects on functional outcome were included; those reporting on angiographic or other imaging studies were excluded. Case reports, reviews, and articles that were not obtainable in full-text or in English were also excluded.

The search yielded 1294 results, of which only 14 met the selection criteria (Table 3).[15–28] No additional studies were identified checking the reference lists. Of the 14 studies (totalling 490 patients), 9 (with 324 patients) had a prospective design, but none had a control or comparison group. Numbers of included patients ranged from 4 to 95. The definition of DCI differed between studies with some studies also including patients without clinical signs of DCI. The intervention also differed substantially between studies, with some studies also using prophylactic or therapeutic hypervolemia besides therapeutic induced hypertension. Furthermore, in several studies, nonresponders to induced hypertension were additionally treated with positive inotropic medication, balloon angioplasty, or vasodilators, such as papaverine and milrinone. In the 14 studies, information on clinical response to the intervention was provided in 9 (187 patients), information on long-term functional outcome in 5 (141 patients), and information on complications because of the intervention in 7 studies (285 patients).

In the 9 studies with 187 patients reporting on clinical response to the intervention, improvement of neurological deficits ranged from 50% to 100%, with most studies reporting improvement in around 80% of patients. In the

Table 2. Search String

(((((((subarachnoid haemorrhage[Title/Abstract]) OR subarachnoid hemorrhage[Title/Abstract]) OR intracranial arterial aneurysms[Title/Abstract]) OR intracranial aneurysms[Title/Abstract]) OR intracranial aneurysm[Title/Abstract]) OR intracranial arterial aneurysm[Title/Abstract]))
AND ((((((((((((((((((((((delayed cerebral ischemia[Title/Abstract]) OR delayed cerebral ischaemia[Title/Abstract]) OR delayed ischemia[Title/Abstract]) OR delayed ischaemia[Title/Abstract]) OR ischemic deficits[Title/Abstract]) OR ischemic deficit[Title/Abstract]) OR ischaemic deficits[Title/Abstract]) OR ischaemic deficit[Title/Abstract]) OR delayed ischemic neurological deficit[Title/Abstract]) OR delayed ischaemic neurological deficit[Title/Abstract]) OR delayed ischemic neurological deficits[Title/Abstract]) OR delayed ischaemic neurological deficits[Title/Abstract]) OR vasospasm[Title/Abstract]) OR symptomatic vasospasm[Title/Abstract]) OR cerebral perfusion[Title/Abstract]) OR delayed neurological deterioration[Title/Abstract]) OR cerebral blood flow[Title/Abstract]) OR cerebral vasospasm[Title/Abstract]) OR delayed cerebral vasospasm[Title/Abstract]) OR delayed ischemic neurological deterioration[Title/Abstract]) OR delayed ischaemic neurological deterioration[Title/Abstract]))
AND ((((((((((((((((((((induced hypertension[Title/Abstract]) OR hypertension[Title/Abstract]) OR triple-H[Title/Abstract]) OR triple-H therapy[Title/Abstract]) OR triple H therapy[Title/Abstract]) OR triple H[Title/Abstract]) OR induced arterial hypertension[Title/Abstract]) OR arterial hypertension[Title/Abstract]) OR blood pressure[Title/Abstract]) OR blood pressure augmentation[Title/Abstract]) OR volume expansion therapy[Title/Abstract]) OR hyperdynamic[Title/Abstract]) OR vasopressor[Title/Abstract]) OR vasopressors[Title/Abstract]) OR hypervolemic[Title/Abstract]) OR hemodynamic augmentation[Title/Abstract]) OR haemodynamic augmentation[Title/Abstract]) OR vasopressor-induced hypertension[Title/Abstract]) OR hypervolaemic[Title/Abstract])

For EMBASE and Cochrane: [Title/Abstract] was replaced by:ti,ab.

Table 3. Characteristics of Included Studies

Reference	Prospective	Nr. Int/No Int.	Control Group	DCI Definition	Intervention	Clinical Response	Functional Outcome	Complications
Roy et al[26]	–	63/0	–	Clinical deterioration not attributable to other causes.	iHT with PE or NE. Nonresponders (n=34) were additionally treated with endovascular therapy.	49 (82%).	Good outcome 3 mo: 31 (49%).	Cardiac arrhythmia: 31 (49%) ECG changes: 29 (46%); troponin elevation: 9 (14%); pulmonary edema: 15 (24%). Death during admission: n.a.
Murphy et al[22]	–	13/0* (2 patients received iHT prophylactically).	–	Clinical deterioration not attributable to other causes.	iHT with NE. One patient was additionally treated with intra-arterial milrinone.	n.a.	Good outcome 3 mo: 6 (46%)	n.a. Death during admission: n.a.
Frontera et al[17]	+	95, of whom 81 received iHT/0	–	Clinical deterioration not attributable to other causes, with associated vasospasm on DSA.	Hypervolemia followed by iHT with PE or NE. Nonreceived inotropes and blood transfusions (number not provided). Twenty-seven patients underwent balloon angioplasty.	Unclear, as this was only assessed for patients with poor outcome.	Good outcome 3 mo: 49 (52%).	n.a. Death during admission: 26%
Raabe et al[25]	+	45/0	–	Clinical deterioration not attributable to other causes or impending cerebral ischemia as indicated by tissue oxygenation, SSEPs, or TCD ultrasonography findings, with associated vasospasm on DSA.	Stepwise protocol: moderate iHT with NE or dopamine, followed by either increased iHT or addition of hypervolemia.	n.a.	Good outcome 6 mo: 17 (38%).	Hyponatremia: 1 (2%); cardiac arrhythmia: 2 (4%); pulmonary edema: 3 (7%); brain edema: 2 (4%). Death during admission n.a.
Aiyagari et al[15]	–	12/0	–	Clinical deterioration not attributable to other causes.	Fluids, PE, dopamine, or dobutamine.	6 (50%).	n.a.	Cardiac arrhythmia: 2 (17%). Death during admission: n.a.
Qureshi et al[24]	–	70/0	–	Clinical deterioration not attributable to other causes, with associated vasospasm on DSA or TCD ultrasonography.	Hypervolemia (n=70) and iHT (n=67) using intravenous vasopressors. Twenty-four patients also received papaverine or angioplasty.	n.a.	Good outcome 2 mo: 38 (54%).	n.a. Death during admission: 20%
Miller et al[20]	+	24/0	–	Clinical deterioration not attributable to other causes.	Hypervolemia and iHT with PE and in 4 patients also dopamine and dobutamine. Eight patients also received papaverine.	21 (88%).	n.a.	CK-MB elevation: 1 (4%); T-wave inversion: 1 (4%); increasing bradycardia: 1 (4%); pulmonary edema of whom 4 symptomatic: 9 (38%). Death during admission: 0%

(*Continued*)

Table 3. Characteristics of Included Studies

Reference	Prospective	Nr. Int/No Int.	Control Group	DCI Definition	Intervention	Clinical Response	Functional Outcome	Complications
Swift and Solomon[27]	–	8/0	–	Clinical deterioration with exclusion of postoperative hemorrhage or hydrocephalus.	Reinstitution of hypervolemia and iHT with dopamine or PE.	Not clear, data not provided for all 8 patients.	n.a.	n.a. Death during admission: 25%
Touho et al[28]	+	8/0	–	Clinical deterioration and proven vasospasm on angiography.	iHT with dopamine.	7 (88%).	n.a.	n.a. Death during admission: 0%
Otsubo et al[23]	+	41/0	–	Clinical deterioration with associated vasospasm on DSA or TCD ultrasonography.	iHT with dopamine and dobutamine.	22 (54%).	n.a.	Hemorrhagic infarction: 4 (10%); intracranial hematoma: 3 (7%); rebleeding from previously clipped aneurysm: 1 (2%); coagulopathy: 3 (7%); cardiac arrhythmia: 3 (7%); pulmonary edema: 1 (2%). Death during admission: 0%
Awad et al[16]	+	42/0	–	Clinical deterioration not attributable to other causes than DCI.	Hypervolemia, hemodilution, and iHT with dopamine or other vasopressors. iHT was only instituted in 16 patients.	25 (60%).	n.a.	Pulmonary edema: 3 (7%); rebleeding from untreated symptomatic aneurysm: 1 (2%). Death during admission: 17%
Muizelaar and Becker [21]	+	4/0	–	Clinical deterioration.	iHT with PE.	4 (100%).	n.a.	n.a. Death during admission: 0%
Kassel et al[18]	+	58/0	–	Clinical deterioration, with associated vasospasm on DSA.	Hypervolemia and iHT with dopamine, dobutamine, NE, metaraminol, isoprotenerol, and vasopressors.	47 (81%).	n.a.	Pulmonary edema: 10, of whom 2 symptomatic: (17%); hyponatremia: 2 (3%); rebleeding from untreated symptomatic aneurysm: 3 (5%); coagulopathy: 2 (3%); hemathorax: 1 (2%); myocardial infarction: 1 (2%). Death during admission: 3%
Kosnik and Hunt[19]	+	7/0	–	Clinical deterioration.	iHT with NE.	6 (86%).	n.a.	n.a. Death during admission: 14%

DCI indicates delayed cerebral ischemia; DSA, digital substraction angiography; iHT, induced hypertension; Int, intervention; n.a., not assessed; NE, norepinephrine; Nr., number of patients; PE, phenylephrine; SSEP, somato sensory evoked potential; and TCD, transcranial Doppler ultrasonography.

*Twelve patients received no iHT and were used as a control group. However, because these patients had no DCI, they could not serve as a control group for assessing effectiveness of therapeutically induced hypertension.

5 studies with 141 patients reporting on long-term functional outcome, a good functional outcome at 2 to 6 months was seen in 38% to 54% of patients. The reported complications from 7 studies (285 patients) are all shown in Table 3. Serious complications, such as cardiac arrhythmia, pulmonary edema, hemorrhagic transformation, and intracranial bleeding occurred in 2% to 49%, with death occurring in 0% to 26%.

These numbers are comparable to our rates of improvement and complications during induced hypertension. The early

clinical improvement after induced hypertension in these case series may explain why induced hypertension has been perceived and recommended as an effective treatment. However, as we found in our trial, early clinical improvement after induced hypertension does not always confer to a good outcome, and early clinical improvement occurs without induced hypertension.

Our study has limitations that need to be addressed. The most important limitation is the limited power because of the smaller study population size than planned. We can, therefore, not exclude a potential overall benefit of induced hypertension. Another limitation is the large number of patients who were excluded from the trial either because of ineligibility or because of declined informed consent. Strength of the study is the randomized controlled design allowing more firm conclusions on the effect of induced hypertension than in previous studies.

A possible benefit of induced hypertension on DCI could be limited to a certain subgroup of patients with aSAH. It is, however, unclear what the characteristics of this subgroup would be. Similarly, some subsets of patients may be more prone to complications from induced hypertension. From our study, we could not identify such a subgroup. Patients with preexisting cardiopulmonary disease are likely to be at increased risk of developing more serious complications from induced hypertension, but as a past medical history of cardiopulmonary disease was an exclusion criterion for our trial, we have no data to substantiate this.

Other possible explanations for not finding a difference in efficacy are insufficient increase in blood pressure, too late initiation, or too short duration of the treatment. Furthermore, the difference in management location between the treatment groups (ICU versus ICU or neuro-medium care unit) might have influenced outcome. In addition, as the clinical diagnosis of DCI can be difficult, we might have included patients whose clinical deterioration was not caused by DCI even though we thoroughly tried to exclude other causes. Alternatively, an explanation is that indeed induced hypertension is not effective because other factors than vasospasm alone play an important role in the development of DCI, such as cortical spreading ischemia and microvasculature disturbances.[29] This explanation is supported by our previously published lack of efficacy of induced hypertension to improve overall cerebral perfusion.[5]

Ideally, given the uncertainty on efficacy on clinical outcome and the risk of complications in our trial, a larger randomized trial to evaluate the effectiveness of induced hypertension should be undertaken. However, since enrolment has been proven difficult, such a trial would require a large number of participating centers and thus would probably imply a large international effort. Alternatively, when further research can establish which patients have a high potential for effect and low risk of complications of induced hypertension, a trial on this subgroup of patients may be more feasible with less subjects.

In conclusion, induced hypertension is a labor-intensive treatment that requires patients to be admitted to an ICU with intensive monitoring. Despite its widespread application, there is still no evidence that induced hypertension improves outcome in patients with DCI, whereas all studies, including our own, show a high rate of serious complications associated with induced hypertension. Considering the results of the current trial, the absence of any other comparative studies and the lack of effect on cerebral perfusion, the widespread use of induced hypertension in aSAH patients with DCI and the pertinent guideline recommendations may require reconsideration.

Appendix

University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands: Ale Algra, Jan-Willem Dankbaar, Celine S. Gathier, Jozef Kesecioglu, Gabriel J.E Rinkel, Irene C. van der Schaaf, Arjen J.C. Slooter, Bon H. Verweij (26 patients); Erasmus MC University Medical Center, Rotterdam, the Netherlands: Ruben Dammers, Diederik W.J. Dippel, Clemens M.F. Dirven, Mathieu van der Jagt, Fop van Kooten, Aad van der Lugt (8 patients); Academic Medical Center Amsterdam, the Netherlands: Walter M. van den Bergh (currently: University Medical Center Groningen, the Netherlands), Bert A. Coert, Janneke Horn, Marcella C. Müller, W. Peter Vandertop (5 patients); Elisabeth-TweeSteden Hospital (ETZ), Tilburg, the Netherlands: Gus N. Beute, Annemarie W. Oldenbeuving, Bram van der Pol, Gerwin Roks, Willem Jan J. van Rooij, Menno Sluzewski (2 patients).

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Data Safety Monitoring Board members include Kit C.B. Roes (chair, biostatistician, University Medical Centre Utrecht, the Netherlands), Jacinta J. Maas (neurologist-intensivist Leiden University Medical Centre, the Netherlands), and Astrid W.E. Hoedemaekers (internist-intensivist Radboud Medical Centre Nijmegen, the Netherlands).

Disclosures

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