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Induced Hypertension in Preventing Cerebral Infarction in Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

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Background and Purpose—Delayed cerebral ischemia (DCI) is an important cause of poor outcome after aneurysmal subarachnoid hemorrhage. If clinical signs of DCI occur, induced hypertension is a plausible but unproven therapeutic intervention. There is clinical equipoise if the use of hypertension induction is useful or not with the consequence that this strategy is irregularly used. We explored the effect of blood pressure augmentation in preventing cerebral infarction in patients with clinical signs of DCI.

Methods—We performed a retrospective observational study, totaling 1647 patients with aneurysmal subarachnoid hemorrhage admitted at 3 academic hospitals in the Netherlands between 2006 and 2015. To study the primary outcome DCI related cerebral infarcts, we only included patients with no cerebral infarct at the time of onset of clinical signs of DCI. Cox regression was used to test the association between induced hypertension after onset of clinical signs of DCI and the occurrence of DCI related cerebral infarcts. Logistic regression was used to relate hypertension induction with poor outcome after 3 months, defined as a modified Rankin score >3. Results were adjusted for treatment center and baseline characteristics.

Results—Clinical signs of DCI occurred in 479 (29%) patients of whom 300 without cerebral infarction on computed tomography scan at that time. Of these 300 patients, 201 (67%) were treated with hypertension induction and 99 were not. Of the patients treated with hypertension induction, 41 (20%) developed a DCI related cerebral infarct compared with 33 (33%) with no induced hypertension: adjusted hazard ratio, 0.59; 95% CI, 0.35 to 0.99. Hypertension induction also prevented poor outcome: adjusted odds ratio, 0.27; 95% CI, 0.14 to 0.55.

Conclusions—Hypertension induction seems an effective strategy for preventing DCI related cerebral infarcts if not already present at the time of onset of clinical signs of DCI. This may lead to a reduction in poor clinical outcome. (*Stroke*. 2018;49:2630-2636. DOI: 10.1161/STROKEAHA.118.022310.)

Key Words: blood pressure ■ cerebral infarction ■ hypertension ■ patients ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (SAH) has an incidence of 6 to 7 per 100 000 person-years in most populations and accounts for 5% of all strokes. Half of the patients are younger than 55 years, and poor outcome exceeds 50%.¹ The most important cause of poor outcome in patients who survive the first 24 hours is delayed cerebral ischemia (DCI), which develops predominantly 4 to 10 days after SAH in ≈30% of survivors.² To date, the L-type calcium channel antagonist nimodipine has been the only intervention proven to be effective in preventing DCI after SAH.³

Several factors, such as angiographic vasospasm, microcirculatory constriction, microthrombosis, cortical spreading depression, and delayed cell apoptosis, are postulated to be associated with the occurrence of DCI. Loss of or abnormal autoregulation by conducting microvasculature, variations in collateral and anastomotic blood flow, and metabolic and (epi) genetic variations determine if angiographic vasospasm leads

to tissue hypoxia and thus DCI. The final common pathway of the cause leading to DCI is a decrease in cerebral blood flow (CBF). Clinical signs of DCI may occur when the CBF and thus the delivery of oxygen no longer meets the demand of the brain tissue in the setting of impaired cerebrovascular autoregulation.⁴

After clinical signs of DCI occur, induced hypertension is a plausible but unproven therapeutic intervention.^{5,6} The primary rationale for the use of induced hypertension is that raising perfusion pressure may increase CBF in high-resistance vascular beds, increase collateral flow to ischemic brain regions, or both and, therefore, elevate brain tissue oxygenation.⁵ However, its presumed effectiveness is based on uncontrolled case-series only.⁷ Furthermore, findings from our randomized controlled trial (RCT) did not support the use of induced hypertension to augment overall CBF in SAH patients with clinical signs of DCI.⁸ However, a small effect cannot be

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definitively excluded because a trend was seen in improved CBF in areas with lowest perfusion. This might be of clinical interest, as hypoperfused areas might progress to infarction if not treated. Induced hypertension might thus be beneficial in improving CBF in regions with impaired perfusion.

In the participating centers of the current study, there is clinical equipoise if therapeutic hypertension induction is beneficial. There is a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment (hypertension induction or not). As a consequence, some centers use hypertension induction when clinical signs of DCI occur while others do not, and even within centers, there is clinical equipoise between physicians. This provides the opportunity to study the effect of hypertension induction.

The objective of this study was to determine if induced hypertension could prevent DCI related cerebral infarcts and subsequent poor outcome when used after clinical signs of DCI occur with no concomitant ischemic lesion at brain computed tomography (CT).

Methods

Data Availability

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

Study Design and Population

In this retrospective observational study, we included adult patients with aneurysmal SAH admitted to the Intensive Care Unit of the Academic Medical Center Amsterdam, University Medical Center Groningen, or University Medical Center Utrecht in the period between 2006 and 2015. Ethical approval was obtained from the Medical ethics committee from the University Medical Center Groningen, and the need for patient consent was waived (METc 2014/154). Patients with SAH were identified by disease codes as registered in the Dutch National Intensive Care Evaluation. Retrieval of subjects was cross-checked with the intensive care unit patient data management system. In the National Intensive Care Evaluation registry database, patient characteristics, presence of chronic disease and comorbidity, reason for admission, disease, intensive care unit course, and outcome characteristics are prospectively collected.⁹

Inclusion criteria were: (1) age 18 years or older; (2) subarachnoid blood on CT scan; and (3) a ruptured intracranial aneurysm as the presumed cause of spontaneous SAH, preferably demonstrated by digital subtraction angiography or CT angiography. Patients with nonaneurysmal, for example, perimesencephalic or traumatic SAH were excluded.

All patients were kept under close observation with continuous monitoring of blood pressure, heart rate, ECG, and arterial oxygen saturation. They were treated according to a standardized protocol that consisted of strict bed rest until aneurysm occlusion, administration of oral nimodipine, cessation of antihypertensive medication, and intravenous administration of fluid aimed at maintaining normovolemia.

Aneurysm occlusion was performed as soon as possible but was postponed in case of a poor clinical condition.

Practice differed between centers and in time, but in general, clinical signs of DCI were treated with intravenous fluid aiming to restore possible hypovolemia. If blood pressure augmentation was initialized, norepinephrine was the vasopressor of choice in all 3 hospitals. The target was usually set at 20 mm Hg above the baseline mean or systolic blood pressure and then increased stepwise in a goal-directed fashion and titrated to clinical response, to a maximum systolic blood pressure of 220 mm Hg. Hypertension induction was tapered in patients not showing any clinical response after 24 hours at this maximum blood pressure but continued for 3 days in case any clinical improvement

occurred. There were several reasons for not using hypertension induction as a strategy to prevent cerebral infarction. Some centers use hypertension induction when clinical signs of DCI occur, whereas others do not, but this changed over time even within centers.

Data Collection and Outcomes

Because this study only involved the anonymized retrospective evaluation of clinical parameters and imaging acquired during routine clinical care, informed consent was waived by the institutional Medical Ethics Committees of all 3 hospitals.

Data were extracted from the electronic medical files, such as clinical condition at admission, clinical signs of DCI, and treatment of the aneurysm. Detailed disease-related information, such as amount of blood on the first CT scan, acute hydrocephalus, location of the aneurysm responsible for SAH, and recurrent bleeding, was assessed by studying all available brain imaging.

Clinical condition on admission at the tertiary center was assessed with the World Federation of Neurological Surgeons grading scale.¹⁰ Poor neurological condition was defined as a World Federation of Neurological Surgeons IV or V.

The amount of subarachnoid blood at the admission CT scan was assessed using Hijdra sum scores, ranging from 0 to 30 for cisternal amount of blood and from 0 to 12 for ventricular amount of blood.¹¹

We quantified the size of the frontal horns of the lateral ventricles by means of the bicaudate index on all CT scans made within 72 hours after SAH. To calculate age-adjusted relative sizes, the bicaudate indexes were divided by the corresponding upper limit per age group (95th percentile for age). Hydrocephalus was defined as an age-adjusted relative bicaudate index above 1.¹² Acute hydrocephalus was considered present if any of the CT scans performed within the first 72 hours after the hemorrhage met this CT-defined criterion.

Recurrent bleeding was defined as an episode of sudden clinical deterioration with evidence of fresh blood on CT scan in comparison with a previous scan. If no CT scan was performed after a highly suggestive clinical history, for example, fresh blood from a liquor drain, this was also scored as recurrent bleeding.

Clinical DCI was defined as a decrease of at least 1 point on the Glasgow Coma Scale sumscore or development of new focal neurological deficits lasting at least 1 hour, or both, with exclusion of any other cause for neurological deterioration (eg, increasing hydrocephalus, recurrent bleeding, clinical signs of epilepsy, presence of an infectious disease, hypoglycemia (serum glucose <3.0 mmol/L), hyponatremia (serum sodium <125 mmol/L), or metabolic encephalopathy because of renal or hepatic failure). The time of onset of clinical signs of DCI and the time of onset of hypertension induction were extracted from the medical files.

The primary outcome was a DCI related cerebral infarct that occurred >1 day after clinical signs of DCI, defined as the presence of a new hypodensity on CT-cerebrum within 30 days after admission, without any other explanation than DCI.¹³ The reason to include only patients without ischemic lesions on brain CT within 1 day after clinical signs of DCI occurred was that it is unlikely that these very early infarctions could be prevented by induced hypertension.

The secondary outcome was poor functional outcome after 3 months, defined as a modified Rankin score of 4, 5, or dead. The Rankin score was assessed by trained research nurses using a structured telephonic interview or during the patient's visit at the outpatient department when it was around 3 months after the SAH.

Statistical Analysis

Patient baseline characteristics are presented as means with SD for continuous, normally distributed variables, and medians with interquartile range for continuous skewed parameters or frequencies (%) for categorical variables. Differences in baseline characteristics between patients with and without DCI related cerebral infarcts were assessed using the independent sample *t* test (for normally distributed continuous variables) or χ^2 test (for categorical factors).

The relation between induced hypertension and the occurrence of DCI related cerebral infarcts on brain CT in patients with clinical signs of DCI was assessed using a Cox regression model, which yields a hazard ratio (HR) with corresponding 95% CI.

To test the relation between induced hypertension for treatment of clinical signs of DCI and poor outcome at 3 months, logistic regression was used, which yields an odds ratio with corresponding 95% CI. In both the Cox regression as the logistic regression model outcomes were adjusted for treatment center and all baseline and disease characteristics shown in Table 1.

To assess if patient characteristics are able to predict prevention of cerebral infarction in patients with hypertension induction after clinical signs of DCI, we performed a stepwise regression analysis using a *P* value of 0.20 to eliminate variables with the

backward method. The full model consists of patient and baseline characteristics mentioned in Table 1 with the exception of treatment center in patients treated with hypertension induction.

Results

Between 2006 and 2015, 2561 SAH patients were admitted in the 3 participating hospitals. In 1722 patients, data were available for the occurrence of clinical signs of DCI and DCI related infarct. In 27 patients, it was unknown whether induced hypertension was applied, and in another 48 patients, hypertension induction was used without clinical signs of DCI leaving 1647 patients eligible for statistical analyses (Figure 1).

Table 1. Baseline and Disease Characteristics of the Complete Cohort (n=1647) and Patients With Clinical Signs of DCI and No Concomitant Cerebral Infarct (n=300) and the Relation Between These Characteristics and the Occurrence of a DCI Related Cerebral Infarct

	All Patients n=1647	Patients With Clinical Signs of DCI			P Value
		Patients With Clinical Signs of DCI n=300	No Development of DCI Related Cerebral Infarct n=226	Development of DCI Related Cerebral Infarct n=74	
Mean age (SD)	56 (13)	56 (12)	56	56	0.88
Female sex	1131 (70%)	221 (74%)	168 (74%)	53 (71%)	0.65
Poor clinical condition at admission (WFNS 4–5)	719 (45%)	128 (43%)	97 (43%)	31 (42%)	0.88
Amount of blood on first CT scan (IQR)					
Median cisternal blood	23 (13–29)	25 (17–29)	21	24	0.006
Median ventricular blood	2 (0–6)	2 (0–5)	3	4	0.097
Acute hydrocephalus	635 (42%)	115 (42%)	79 (35%)	36 (49%)	0.11
Location aneurysm					
Anterior circulation	1267 (77%)	261 (87%)			
Posterior circulation	243 (15%)	33 (11%)	20 (9%)	13 (18%)	0.005
No aneurysm found	50 (3%)	6 (2%)			
Unknown	87 (5%)	...			
Treatment type					
Endovascular	722 (44%)	175 (59%)	128 (57%)	47 (64%)	...
Clip	539 (33%)	115 (39%)	94 (42%)	21 (28%)	0.09
None	313 (19%)	4 (1%)	2 (<1%)	2 (2%)	0.31
No aneurysm found	50 (3%)	6 (2%)	2 (<1%)	4 (5%)	0.03
Unknown	23 (1%)	...			
Recurrent bleeding					
Total	303 (18%)	36* (12%)	24 (11%)	12 (16%)	0.58
CT proven	248 (15%)	27 (9%)			
Clinically	55 (3%)	9 (3%)			
Clinical signs of DCI	479 (29%)	300			
Median day clinical signs of DCI (IQR)	6 (3–9)	6 (3–9)			
DCI related cerebral infarction	272 (17%)	74 (25%)			
Median day DCI related cerebral infarction (IQR)	7 (4–11)	4 (2–7)			
Hypertension induction	269 (56%)†	201 (67%)			

CT indicates computed tomography; DCI, delayed cerebral ischemia; IQR, interquartile range; SD, standard deviation; and WFNS, World Federation of Neurological Surgeons.

*Four patients had recurrent bleeding during induced hypertension.

†Of all 479 patients with clinical symptoms of DCI.

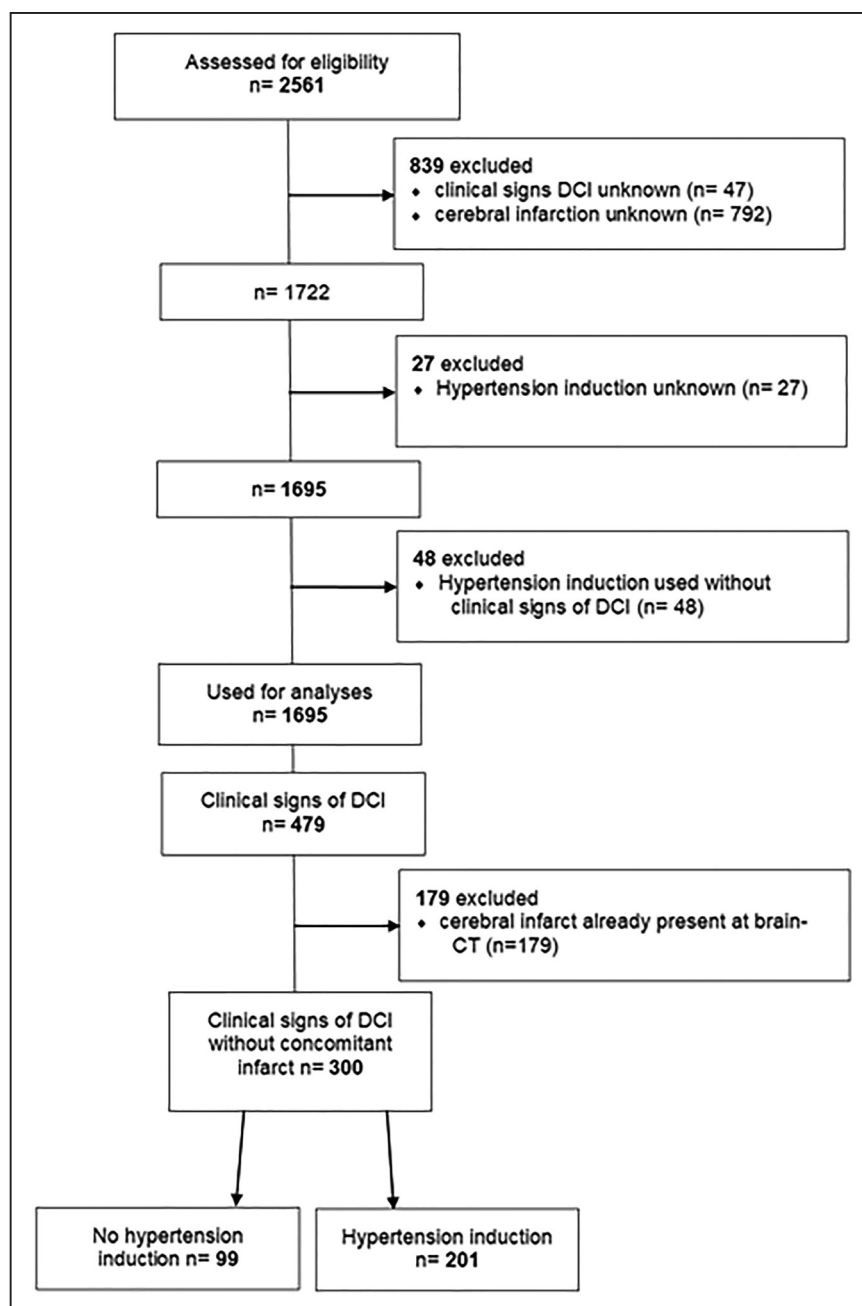


Figure 1. Flowchart of included patients. CT indicates computed tomography; and DCI, delayed cerebral ischemia.

Patients were equally distributed between the 3 participating hospitals (range, 31%–36%).

Baseline and disease characteristics of these patients are shown in Table 1. Clinical signs of DCI occurred in 479 (29%) patients of whom 272 (57%) eventually developed a DCI related cerebral infarct. However, in 179 patients, cerebral ischemia was already present at brain CT at the time clinical signs of DCI were detected, and these patients were excluded for the primary analyses. Baseline and disease characteristics of the remaining 300 patients and the relation with the occurrence of a cerebral infarct after clinical signs of DCI is also shown in Table 1. Patients who developed a DCI related cerebral infarct after clinical signs of DCI harbored more frequent an aneurysm in the posterior cerebral circulation and had a larger amount of subarachnoid blood.

In 201 (67%) of the 300 patients, hypertension was induced, and in the remaining 99 (33%) patients, hypertension was not induced. Of the 201 patients treated with induced hypertension, 41 (20%) developed a DCI related cerebral infarct ≥ 1 day after clinical signs of DCI occurred compared with 33 (33%) with no induced hypertension (Table 2). With induced hypertension, the crude HR for DCI related cerebral infarction was 0.54; 95% CI, 0.34 to 0.86 and after adjustment, 0.59; 95% CI, 0.35 to 0.99 (Table 3).

To illustrate the DCI related cerebral infarct free interval after clinical signs of DCI with or without induced hypertension survival curves are shown in Figure 2.

In patients who developed a DCI related cerebral infarct after clinical signs of DCI 48 (74%) had a poor outcome compared with 64 (36%) in patients in whom clinical signs did not

Table 2. Occurrence Cerebral Infarct With or Without Induced Hypertension After Onset of Clinical Symptoms of DCI Without Concomitant Infarct (n=300)

		Hypertension Induction		P Value
		No (99)	Yes (201)	
DCI related cerebral infarct	No (226)	66	160	0.015
	Yes (74)	33 (33%)	41 (20%)	

DCI indicates delayed cerebral ischemia.

lead to cerebral infarction ($P<0.001$; Table 4). With induced hypertension, the adjusted odds ratio for poor outcome was 0.27; 95% CI, 0.14 to 0.55 (Table 3).

With the stepwise backward regression analyses, we found that only the amount of subarachnoid blood independently predicts the prevention of a DCI related cerebral infarct (HR, 0.95; 95% CI, 0.90–0.99) in patients treated with hypertension induction. Female sex (HR, 0.59; 95% CI, 0.27–1.29) and posterior location of the aneurysm (HR, 0.47; 95% CI, 0.20–1.08) were the last remaining nonstatistically significant variables in the model.

Discussion

The findings of our study suggest that hypertension induction has a role in preventing DCI related cerebral infarcts after clinical signs of DCI have occurred. Preventing cerebral infarction by means of induced hypertension may also reduce poor outcome. Patients who developed DCI related cerebral infarcts had larger amount of subarachnoid blood and more frequent a posterior location of the aneurysm. The regression analysis confirmed a role for the amount of subarachnoid blood to predict DCI related infarction in patients treated with induced hypertension. Patients with more subarachnoid blood have less chance for prevention of cerebral infarction with induced hypertension. Although the amount of subarachnoid blood is a well-known risk factor for DCI, our study was not designed to prove an association with the development of a DCI related cerebral infarct after clinical signs of DCI has occurred. We did not cross-validate our stepwise regression model by splitting the data. Validation of the model should be performed in another, preferably prospective, dataset. The underlying pathogenesis and the possible effect of female sex and aneurysm location for development of DCI related cerebral infarcts should also be subject of further studies.

Despite its widespread application, there is no evidence that induced hypertension improves outcome in patients with DCI. The only RCT thus far did not add any evidence to support induced hypertension.¹⁴ No observational

study of this scale has been performed to support its beneficial effect. Several observational studies exist, but none had a control or comparison group, and the largest study numbered 95 patients.^{15–28} Most studies focused on clinical response to the intervention, whereas information on long-term functional outcome is scarce. Improvement of neurological deficits ranged from 50% to 100%, with most studies reporting improvement in around 80% of patients. None of the studies provided information on preventing DCI related cerebral infarcts.

Induced hypertension is hardwired in clinical practice and in international guidelines, but its impact on outcome has not yet been submitted to the scrutiny of an RCT. This was the aim of our multicenter RCT that was terminated prematurely because of slow recruitment that reduced power for the primary end point clinical outcome after 3 months.¹⁴ The results from that study did not add any evidence to support induced hypertension and show that this treatment can lead to serious adverse events. Furthermore, there was no difference in global CBF between patients treated with hypertension induction or not.⁸ The conduction of a large clinical trial with sufficient power seems challenging given the lack of clinical equipoise in the international community. Further research should focus on better selection of patients that might benefit from hypertension induction. Selection of eligible patients might be accomplished with use of multimodality monitoring, for example, transcranial Doppler, EEG, or near-infrared spectroscopy, that may detect DCI before clinical signs occur and, therefore, might improve the effect of this therapy as in many cases a cerebral infarct was already present at that time.

There are several limitations to this study; the most obvious being the retrospective nature of this study, which prevents us from making definitive conclusions. The major limitation of our study is that the reason for the treating physician to use hypertension induction or not is unknown. It seems likely that certain physicians always use hypertension induction, whereas others are more reluctant and that this difference is largely

Table 3. Occurrence of Cerebral Infarct and Poor Outcome Related to Hypertension Induction in Patients With Clinical Symptoms of DCI Without Concomitant Infarct (n=300)

	Occurrence of Cerebral Infarct		Poor Outcome*	
	Crude HR (95% CI)	Adjusted HR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Hypertension induction	0.54 (0.34–0.86)	0.59 (0.35–0.99)	0.39 (0.23–0.66)	0.27 (0.14–0.55)

DCI indicates delayed cerebral ischemia; and OR, odds ratio.

*Analysis includes 244 patients; of 56 patients outcome at 3 mo is missing.

†Adjusted for treatment center and all baseline and disease characteristics shown in Table 1.

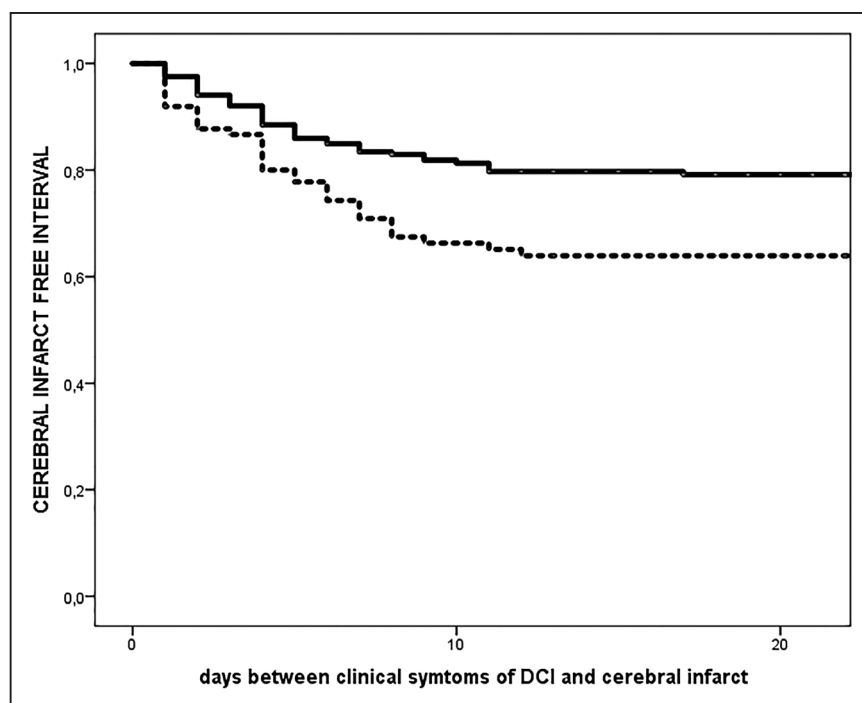


Figure 2. Cerebral infarct free interval after clinical signs of delayed cerebral ischemia (DCI) occur dependent on hypertension induction (n=300). Straight line shows hypertension induction, and dotted line shows no hypertension induction.

based on treatment center policy. For that reason, we included treatment center in our adjusted analyses. A reason not to use hypertension induction may be that the patient already has an elevated blood pressure which makes further augmentation futile. Another reason might be a poor clinical condition of the patient that could have led to withholding intensive treatment like hypertension induction resulting in a self-fulfilling prophecy. Although poor clinical condition at admission did not differ between the treatment groups and adjustment for clinical condition at admission was performed, the clinical situation at the moment of initiating hypertension induction was not known. Finally, brain CT was not routinely performed leading to exclusion of patients for which it was uncertain if the primary end point, cerebral infarction, was reached. Also, patients with an early follow-up CT scan without cerebral ischemia might have developed a DCI related cerebral infarct thereafter. However, all patients with endovascular aneurysm repair had routine follow-up imaging, and the vast majority of the remaining patients had multiple and long-term follow-up brain imaging.

There were some slight differences in treatment protocols for induced hypertension between the 3 participating hospitals, but the aim of this study was to test if hypertension induction was able to prevent cerebral infarction irrespective of nuances in approach. Moreover, adjustment for treatment

center did not change the results. Although adjustment for 9 baseline characteristics (including treatment center) may cause an unstable multivariable model for the primary endpoint DCI related cerebral infarction, reducing it to the most relevant confounders did not change the results either.

Our RCT showed that induced hypertension can lead to serious adverse events.¹⁴ Because of the retrospective design, data on side effects were not available, which is a shortcoming of the current study. In theory, it could, therefore, be possible that patients with poor outcome, despite induced hypertension as treatment for DCI are those patients with severe side effects. However, the results of our study suggest that the benefit of induced hypertension might outweigh the effect of complications.

Conclusions

Because of the retrospective and observational design of the study, no clear statements can be made, but the results suggest that hypertension induction seems an effective strategy to prevent DCI related cerebral infarcts after clinical signs of DCI occurred. This may also lead to a reduction in poor clinical outcome.

Disclosures

None.

Table 4. Poor Outcome After Clinical Symptoms of DCI With or Without Development of Cerebral Infarct ≥ 1 Day After Clinical Symptoms Occur (n=244)*

		Poor Outcome		P Value
		No (132)	Yes (112)	
DCI related cerebral infarct	No (179)	115	64 (36%)	<0.001
	Yes (65)	17	48 (74%)	

DCI indicates delayed cerebral ischemia.

*Of 56 patients outcome at 3 mo is missing.

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