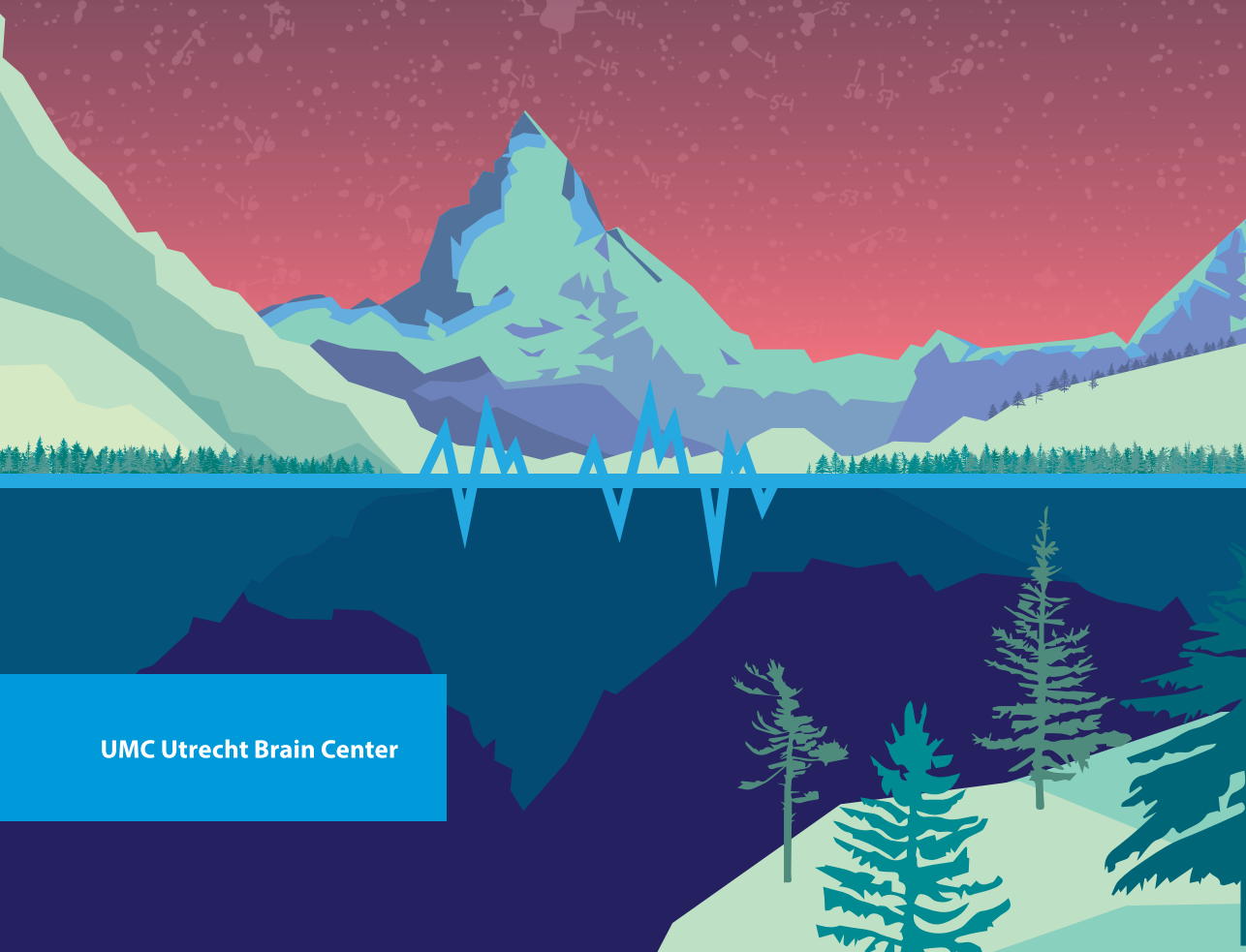
STRATEGIES FOR PREVENTION AND TREATMENT OF DELAYED CEREBRAL ISCHAEMIA AFTER ANEURYSMAL SUBARACHNOID HAEMORRHAGE

Celine Gathier



UMC Utrecht Brain Center

Strategies for prevention and treatment of delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage

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Strategies for prevention and treatment of delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage

Strategieën ter voorkoming en behandeling van secundaire ischemie na
een aneurysmatische subarachnoïdale bloeding

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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Promotoren: Prof. dr. G.J.E. Rinkel
Prof. dr. A.J.C. Slooter

Voor mijn ouders

Ik leef in een groot heelal
Roel Gathier

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PART I

INTRODUCTION

1

General Introduction

INTRODUCTION

Aneurysmal subarachnoid haemorrhage

Aneurysmal subarachnoid haemorrhage (aSAH) is a uncommon type of stroke, accounting for around 5% of all stroke types.[1] Despite being less common than ischaemic stroke and intracerebral haemorrhage, the effect of aSAH on loss of productive years of life is similar to that of ischaemic stroke, due to the young age of those affected and the high case morbidity and fatality.[2] Around 10-15% of patients die before reaching the hospital[3], and those who are admitted are at risk of complications that further worsen the prognosis, such as rebleeding from the aneurysm before it is repaired and delayed cerebral ischaemia. Even after intensive treatment, case fatality after aSAH is as high as 30%[4], and only 36 – 55% of patients regain independency in their daily activities[5]. Further, only a third of patients who were working at the time of aSAH is able to resume their work entirely and another third has to work fewer hours or has to switch to a less responsible position[6,7]. Moreover, cognitive or emotional complaints are reported in up to 95% of patients 3 months after aSAH[6,7] and 50% of patients report ongoing memory disturbances 1 year after aSAH[8]. It is therefore no surprise that patients who have survived an aSAH have, on a group level, a reduced quality of life.[6] Factors associated with an increased risk of poor outcome after aSAH include early brain injury at time of aneurysmal rupture, rebleeding, hydrocephalus, meningitis and delayed cerebral ischaemia.[9]

Delayed cerebral ischaemia

Delayed cerebral ischaemia (DCI) occurs in around 20-30% of aSAH patients, mostly between day 3 and 21 after the initial haemorrhage.[10] It is a feared complication, as it is an independent predictor of poor long-term outcome.[11] In fact, cerebral infarction from DCI remains the most important cause of case morbidity and fatality in patients surviving the initial days after the haemorrhage.[12] The main predictors of DCI are the clinical condition on admission reflecting the impact of the initial ischaemia and the amount of SAH on admission CT scan. However, prediction of DCI remains inaccurate.[13]

Definition of DCI

DCI as outcome event is defined as neurological decline lasting at least one hour, that cannot be attributed to other causes such as rebleeding, hydrocephalus or metabolic disturbances, or as the presence of delayed cerebral infarction on imaging.[14-16] It occurs when cerebral blood flow (CBF) no longer meets the demand of the brain tissue, and was once entirely attributed to "cerebral vasospasm". However, 70% of aSAH patients develop angiographic vasospasm, whereas only 30% of those patients develop clinical symptoms of DCI or cerebral infarction.[11,17] Vice versa, not all patients with DCI have angiographic

vasospasm.[18] Therefore, the pathophysiology of DCI is now hypothesised to be due to combined effects of several factors influencing cerebral blood flow, such as angiographic vasospasm, microcirculatory dysfunction, microthromboembolism, inflammation and cortical spreading ischaemia.[13, 19-23]

Diagnosing DCI

The detection of DCI can be difficult when it starts. Patients that can be monitored clinically can be screened by clinical examination alone[24] but this method may not be suitable for patients who are sedated or who are already neurologically impaired. That is why radiological examinations focused on imaging of the cerebral vasculature and/or quantification of cerebral blood flow are often additionally used to aid in the screening for DCI. The screening protocols for DCI vary enormously among institutions, ranging from clinical examination alone to frequent computed tomography angiography (CTA) and CT perfusion (CTP), doppler ultrasonography, and invasive monitoring.[13,25]

Preventing DCI

As DCI is such a detrimental complication, management after aneurysm occlusion is mainly focused on the prevention of DCI. Prevention is focused on optimizing CBF and avoiding reduction of CBF. This includes prescribing nimodipine (a calcium channel blocker that has been proven to improve outcome, probably through influencing cortical spreading ischaemia and microthromboembolism)[26-28], maintaining normal intravascular volume status, temperature, electrolytes, glucose and adequate cerebral perfusion pressure by maintaining adequate blood pressure.[13,29] Prophylactic use of hypervolaemia[30,31] or balloon angioplasty[32] in order to improve CBF has been found non beneficial in improving outcome after aSAH.

Treating DCI

As DCI still occurs in 20-30% of patients despite these preventative measures, treatment strategies for DCI have been an important subject of research in aSAH patients. In the past, rescue therapy with "triple-H" therapy (hypertension, hypervolaemia, haemodilution) was often installed.[33-35] However, a meta-analysis showed that only induced hypertension seemed capable of improving CBF, with hypervolaemia being associated with increased risk of complications and haemodilution causing a decrease in oxygen delivery to the brain despite increased CBF.[30] Therefore, several international guidelines nowadays advise treating DCI with induced hypertension combined with euvolemia.[29,36]

However, even though induced hypertension is reported to reverse signs of DCI in up to two-thirds of treated patients[37], sound evidence of its effectiveness is lacking and it is unclear whether induced hypertension actually leads to improved functional outcome. Besides, the treatment is associated with serious complications such as pulmonary oedema, cardiac rhythm disorders and posterior reversible encephalopathy syndrome.[38-46]

Alternative rescue therapy with endovascular treatment such as balloon angioplasty is a non-proven treatment which carries a substantial risk of side-effects.[47,48]

To summarise, we are currently able to reduce the risk of DCI only to a minor extent with nimodipine. Other preventative measures have not been shown to improve outcome. Also, current suggested strategies for treatment of DCI are lacking evidence of efficacy on improving functional outcome. Only induced hypertension showed promising results in improving CBF, but it's efficacy on outcome has never been proven in a randomised clinical trial.

Outline of the thesis

The studies underlying this thesis aim to search for new ways to improve the prevention of DCI (part II) and its treatment by means of induced hypertension (part III).

In part II of this thesis we aimed to identify modifiable factors in order to better prevent DCI.

As the amount of blood is associated with the development of DCI[49-51], an automatic and operator-independent quantification method of the amount of blood was developed using non-contrast CT scans of patients with a ruptured middle cerebral artery aneurysm[52]. In **Chapter 2**, we assessed whether the total haemorrhage volume as measured with this new automatic method was independently associated with development of DCI aiming to develop a possible add-on in prediction models of DCI.

It is speculated that low blood pressure is associated with the development of DCI[53-55], and that high blood pressure is associated with the development of rebleeding[56]. However, a clear time dependent relation has not yet been confirmed. In **Chapter 3**, we assessed in aSAH patients admitted to the intensive care unit (ICU) whether lowest blood pressure preceding DCI or highest blood pressure preceding rebleeding was actually associated with these complications, aiming to provide the clinician with better advice on blood pressure management after aSAH.

As the presence of inflammation and infection is also associated with the development of DCI[57-60], we investigated in **Chapter 4** whether treatment with preventive antibiotics in aSAH patients admitted to the ICU was associated with a decreased risk of DCI.

Part III of this thesis focusses on the use of induced hypertension as a treatment strategy for DCI in aSAH patients. Induced hypertension was the only component of the so-called "Triple-H" therapy that seemed promising in increasing CBF in patients with DCI.[30] However, sound evidence of its effect on CBF or on functional outcome was lacking. Therefore, we designed a randomised clinical trial comparing the effectiveness of induced hypertension versus no induced hypertension on improving CBF and functional outcome in DCI patients. The trial was named the "HIMALAIA" trial, which is an acronym for Hypertension Induction in the Management of AneurysmaL subArachnoid haemorrhage with secondary IschaemiA. In **Chapter 5**, the design of the multicenter trial is outlined. **Chapter 6** describes the results of the substudy of the trial in which we investigated the effect of induced hypertension versus no induced hypertension on cerebral perfusion as measured by CTP. **Chapter 7** describes the results of the effect of induced hypertension versus no induced hypertension on functional outcome. Unfortunately, the HIMALAIA trial was halted prematurely due to lack of effect of induced hypertension on cerebral perfusion and slow patient recruitment. In **Chapter 8**, reasons for the slow inclusion rate are reviewed and suggestions for improvement of future research in DCI patients are provided.

In **Chapter 9,** the results as described in this thesis are summarized and critically reviewed, followed by perspectives on future research in DCI patients.

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PART II

FACTORS ASSOCIATED WITH THE DEVELOPMENT OF DCI

2

Association of Automatically Quantified Total Blood Volume after Aneurysmal Subarachnoid Hemorrhage with Delayed Cerebral Ischemia

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ABSTRACT

Background and purpose

The total amount of extravasated blood after aneurysmal subarachnoid hemorrhage (aSAH), assessed with semiquantitative methods such as the modified Fisher and Hijdra scales, is known to be a predictor of delayed cerebral ischemia. However, prediction rates of delayed cerebral ischemia are moderate, which may be caused by the rough and observer-dependent blood volume estimation used in the prediction models. We therefore assessed the association between automatically quantified total blood volume on non contrast computed tomography (NCCT) and delayed cerebral ischemia.

Materials and methods

We retrospectively studied clinical and radiologic data of consecutive patients with aSAH admitted to 2 academic hospitals between January 2009 and December 2011. Adjusted odds ratio's (ORs) with associated 95% confidence intervals were calculated for the association between automatically quantified total blood volume on NCCT and delayed cerebral ischemia (clinical, radiologic, and both). The calculations were also performed for the presence of an intraparenchymal hematoma and/or an intraventricular hematoma and clinical delayed cerebral ischemia.

Results

We included 333 patients. The adjusted OR of total blood volume for delayed cerebral ischemia (clinical, radiologic, and both) was 1.02 (95% CI, 1.01–1.03) per milliliter of blood. The adjusted OR for the presence of an intraparenchymal hematoma for clinical delayed cerebral ischemia was 0.47 (95% CI, 0.24–0.95) and of the presence of an intraventricular hematoma, 2.66 (95% CI, 1.37–5.17).

Conclusions

A higher total blood volume measured with our automated quantification method is significantly associated with delayed cerebral ischemia. The results of this study encourage the use of rater-independent quantification methods in future multicenter studies on delayed cerebral ischemia prevention and prediction.

INTRODUCTION

Delayed cerebral ischemia (DCI) occurs in 20%–30% of patients with aneurysmal subarachnoid hemorrhage (aSAH) and is associated with poor outcome.[1-3] Patients who develop DCI need costly intensive care. The cause of DCI is multifactorial, including larger and smaller vessel vasospasm, cortical spreading ischemia, microvascular dysfunction, and thrombosis.[3] Blood breakdown products in the subarachnoid and CSF spaces may cause vasospasm.[2] Several studies have reported the positive relationship between the total amount of extravasated blood after SAH and the development of vasospasm (at that time considered the main cause of DCI) by using CT grading scales such as the modified/revisited Fisher grading scale and the Hijdra scale.[4-7] These grading scales only provide a rough estimation of the aneurysmal total blood volume (TBV) and are observer-dependent, factors that may add to the moderate prediction rates of DCI.[8] More reliable quantification of TBV might result in better prediction of DCI, which can help clinicians more accurately identify patients at risk and more effectively use scarce resources.[9] To assess the association of TBV with DCI, a reliable and valid method for measuring subarachnoid blood volume is needed, with correction for possible confounding influences. We recently validated a fully automatic method for TBV quantification on NCCT. This method is based on a relative density increase of blood after aSAH in relation to different brain structures.[10] In the current study, we aimed to assess the association of automatically quantified TBV with DCI.

MATERIALS AND METHODS

Patient population

We included consecutive patients with aSAH who were admitted between January 2009 and December 2011 to 2 large university hospitals (Academic Medical Center Amsterdam and University Medical Center Utrecht) in the Netherlands.

"Aneurysmal SAH" was defined as an aneurysmal bleeding pattern with an associated aneurysm. Patients without aneurysms proved on CTA/MRA/DSA were excluded. We further excluded patients with a baseline CT obtained 24 hours after ictus because of the risk of blood clearance and patients in whom the CT scans could not be used for the automatic quantification method because of movement artifacts or metal artifacts caused by previous treatment. Patients with technically inadequate scans (scans in 2 parts or incomplete scans) were also excluded. Patients with an external ventricular drain on the first CT were excluded because of artifacts and possible blood clearance. TBV was defined as the sum of subarachnoid (cisternal and sulcal), intraparenchymal, intraventricular, and subdural blood.

Clinical and Imaging Data Collection

All baseline characteristics of the included patients were collected through retrospective review of the clinical charts by a single observer (C.S.G.). These included age, medical history of hypertension, date of the aSAH ictus, hospital admission date, clinical condition on admission according to the World Federation of Neurosurgical Societies scale (WFNS)[11], NCCT date, the occurrence of rebleeding (clinical, not CT-confirmed, or radiologic), aneurysm location (anterior or posterior circulation), aneurysm treatment (coiling, clipping, or no aneurysm treatment), and date of death. The WFNS score on admission was dichotomized into favorable (1–3) and unfavorable (4 –5). This observer also assessed the presence of clinical DCI, which was defined as clinical deterioration that could not be explained by any cause other than DCI, and radiologic DCI, which was defined as the presence of cerebral infarction on CT or MR images within 6 weeks after SAH or on the latest CT scan or MR image obtained before death, which could not be attributed to other causes such as surgical clipping or endovascular treatment, according to previously published criteria.[12] The patients were followed as long as they were hospitalized.

For the volume analysis, generally the first CT scan (all 5-mm sections) after the aSAH ictus was used. Only in case of a rebleeding within 24 hours and before treatment was the CT scan after rebleeding used because of the larger blood volume. All CT scans were anonymized before assessment (H.A.M. and I.A.Z.) and were thereafter assessed for the appropriateness for automated quantification (I.A.Z.). The TBV (in milliliters) was automatically quantified (Fig 1), and the quality of the automatic segmentation was evaluated by using ITK-SNAP, Version 2.4.0 (www.itksnap. org) (I.A.Z.).[13]

All CT scans were inspected for the presence of intraparenchymal hematoma (IPH) and/or intraventricular hematoma (IVH) (I.A.Z.). The presence or absence of IPH and IVH was scored dichotomously because it was not possible to measure blood volume in separate locations with our automated quantification method. The differentiation between a blood clot in the Sylvian fissure and an IPH was made on the initial CTA (I.A.Z.).[14] All estimates of blood volume and blood location were performed blinded to the presence or absence of DCI.

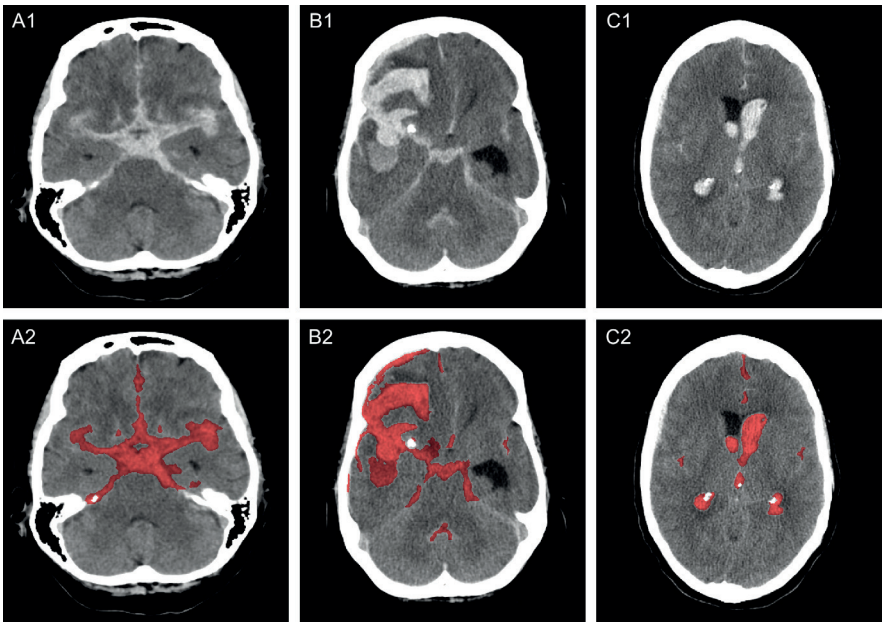

Figure 1. Examples of SAH bleeding patterns on CT (upper), with corresponding segmentations in red as provided by the automatic quantification method (lower).[10] A. SAH with blood in both Sylvian fissures, B. SAH with the presence of IPH, C. SAH with the presence of IVH.

Statistical analysis

Descriptive statistics. Dichotomous variables were presented as percentages. Continuous variables were tested with the Shapiro Wilk test for normal distribution (W 0.9 is considered a normally distributed variable). Normally distributed variables were expressed as means with SDs, and not normally distributed variables were expressed as medians with interquartile ranges (25%– 75%). Normally distributed variables were tested with the Student t test, and not normally distributed variables were tested with the Mann-Whitney U test. Categoric variables were tested by using the Fisher exact test.

Modeling. Logistic regression analysis was used to calculate odds ratios with associated 95% confidence intervals. Bivariable analyses were performed with previously chosen covariables known to be associated with DCI on the basis of the literature to identify important confounders (defined as variables that changed the crude OR from the univariable analysis by 10%).[15] In the multivariable analysis, confounders were added to the univariable model to calculate adjusted odds ratios (aORs) with associated 95% CIs.

As our primary analysis, we assessed the association between TBV and clinical DCI (with or without radiologic DCI), radiologic DCI (with or without clinical DCI), and clinical and radiologic DCI (patients with both clinical and radiologic DCI) combined. Evaluated confounders were age, sex, neurologic status on admission (dichotomized WFNS grade), treatment of the aneurysm (clipping/coiling/no treatment), rebleeding, hypertension, IPH, and IVH.

As a secondary analysis, we assessed the association between blood location (IPH and IVH) and clinical DCI (with or without radiologic DCI). We used clinical DCI as the only outcome variable because we found similar aORs for all 3 outcome variables (clinical DCI, radiologic DCI, and both) in the primary analysis. Evaluated confounders were age, sex, neurologic status on admission (dichotomized WFNS grade), treatment of the aneurysm (clipping/coiling/no treatment), rebleeding, hypertension, blood volume, IPH (in the model with IVH as the central determinant), and IVH (in the model with IPH as the central determinant).

Because patients who die within 3 days after the aSAH ictus have a much lower risk of developing DCI, we performed sensitivity analyses in the subset of patients who survived 3 days after aSAH.

RESULTS

Patient characteristics

We initially evaluated 458 potentially eligible patients with aSAH. Of these, 333 patients were included in the analyses (Fig 2). The mean TBV was 46.1 ± 29.4 mL. Characteristics of the included patients are shown in Table 1.

Sixty-eight (20%) patients had clinical and/or radiologic DCI, 62 (19%) had clinical DCI (with or without radiologic DCI), 40 (12%) had radiologic DCI (with or without clinical DCI), and 34 (10%) had both clinical and radiologic DCI. Twenty-eight (8%) patients had only clinical DCI, and 6 (2%) had only radiologic DCI (Table 2). One (2.1%) patient developed clinical signs of DCI 2 days after the aSAH ictus. There were 102 patients (31%) with IPH, 203 patients (61%) with IVH, and 63 patients (19%) with IPH and IVH combined. Forty-seven (14%) patients died within 3 days of the aSAH ictus. The mean TBV in these patients was 63.0 ± 34.1 mL.

Figure 2. Flow chart of patient inclusion.

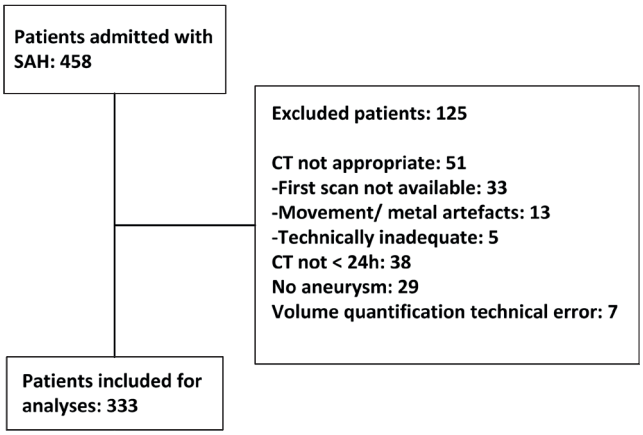

Table 1. Patient characteristics.

	Total Patient group (%)	Patients with Clinical and/or Radiologic DCI	Patients without DCI (%)	*P* value
No.	333	68 (20)	265 (80)	-
Female sex	238 (71)	47 (69)	191 (72)	.653
Age (yr) (mean) (SD)	55.7 (11.9)	56.0 (12.7)	55.7 (11.7)	.828
Hypertension in medical history	88 (26)	24 (35)	64 (24)	.090
WFNS favorable on admission (I-III)	163 (49)	34 (50)	129 (49)	.892
Mean TBV (ml) (SD)[a]	46.1 (29.4)	51.6 (27.3)	44.6 (29.8)	.080
IPH	102 (31)	16 (24)	86 (32)	.185
IVH	203 (61)	51 (75)	152 (57)	.008
IPH and IVH	63 (19)	12 (18)	51 (19)	.863
Rebleed	52 (16)	9 (13)	43 (16)	.708
Anterior circulation	245 (74)	50 (74)	195 (74)	1.000
Posterior circulation	88 (26)	18 (26)	70 (26)	
Neurosurgical treatment[b]	141 (42)	30 (44)	111 (42)	.325
Endovascular treatment[c]	135 (41)	36 (53)	99 (37)	
Death within 3 days	47 (14)	1 (1)	46 (17)	<.001

[a] Automatically quantified total blood volume on noncontrast CT.
[b] Two patients treated with bypass surgery.
[c] One patient treated with stent, and 1 with parent vessel occlusion.

Table 2. Patient characteristics in groups with respect to DCI.

	Patients with Clinical and/ or Radiologic DCI	Patients with Clinical DCI (%)[a]	Patients with Radiologic DCI (%)[b]	Patients with Clinical and Radiologic DCI (%)
No.	68 (20)	62 (19)	40 (12)	34 (10)
Female sex	47 (69)	43 (69)	28 (70)	24 (71)
Age (yr) (mean) (SD)	56.0 (12.7)	55.4 (12.9)	57.9 (12.4)	57.1 (12.8)
Hypertension in medical history	24 (35)	21 (34)	18 (45)	15 (44)
WFNS favorable on admission (I-III)	34 (50)	30 (48)	18 (45)	14 (41)
Mean TBV (mL) (SD)[c]	51.6 (27.3)	52.1 (27.4)	53.2 (28.1)	54.3 (28.3)
IPH	16 (24)	14 (23)	7 (18)	5 (15)
IVH	51 (75)	47 (76)	31 (78)	27 (79)
IPH and IVH	12 (18)	10 (16)	5 (13)	3 (9)
Rebleed	9 (13)	9 (15)	6 (15)	6 (18)
Anterior circulation	50 (74)	45 (73)	28 (70)	23 (68)
Posterior circulation	18 (26)	17 (27)	12 (30)	11 (32)
Neurosurgical treatment[d]	30 (44)	28 (45)	19 (48)	17 (50)
Endovascular treatment[e]	36 (53)	33 (53)	19 (48)	16(47)
Death within 3 days	1 (1)	1 (2)	1 (3)	1 (3)

[a] Clinical DCI with or without radiologic DCI.
[b] Radiologic DCI with or without clinical DCI.
[c] Automatically quantified total blood volume on noncontrast CT.
[d] Two patients treated with bypass surgery.
[e] One patient treated with stent, and 1 with parent vessel occlusion.

Association between blood volume and blood location and DCI in the total group

The aOR (95% CI) of TBV and DCI (clinical, radiologic, both) was 1.02 (1.01–1.03) per milliliter of blood (Table 3). The aOR (95% CI) of IPH and clinical DCI was 0.47 (0.24 –0.95) and of IVH and clinical DCI, 2.66 (1.37–5.17).

Table 3. Associations between blood volume and blood location and DCI in the total group (N = 333).

Dependent variable	Central Determinant	OR (95%CI)	aOR (95% CI)
Clinical DCI (with or without radiologic DCI)	TBV[a]	1.01 (1.0-1.02)[b]	1.02 (1.01-1.03)[b]
	IPH[c]	0.61 (0.32-1.16)	0.47 (0.24-0.95)
	IVH[d]	2.31 (1.23-4.33)	2.66 (1.37-5.17)
Radiologic DCI (with or without clinical DCI)	TBV[e]	1.01 (1.0-1.02)[b]	1.02 (1.01-1.03)[b]
Clinical and radiologic DCI	TBV[f]	1.01 (1.0-1.02)[b]	1.02 (1.01-1.03)[b]

[a] Confounders: age, WFNS, treatment, IPH, and IVH.
[b] Per milliliter of blood.
[c] Confounder: treatment.
[d] Confounders: WFNS and blood volume.
[e] Confounders: age, treatment, IPH, and IVH.
[f] Confounder: treatment, IPH, and IVH.

Sensitivity analysis

In the 286 patients included in the sensitivity analyses, the mean TBV was 43.3 ± 27.6 mL. In the subgroup of patients without clinical DCI, the mean TBV was 40.8 ± 27.2 mL, and in the subgroup of patients with clinical DCI, 52.3 ± 27.5 mL (P .004). IPH occurred in 85 (30%) patients; IVH, in 172 (60%) patients. The association results in the sensitivity analysis (Table 4) are similar to the results in the total group (Table 3).

Table 4. Associations between blood volume and blood location and DCI in patients who survived three days or more (n = 286).

Dependent variable	Central Determinant	OR (95% CI)	aOR (95% CI)
Clinical DCI (with or without radiologic DCI)	TBV[a]	1.01 (1.00-1.03)[b]	1.02 (1.01-1.03)[b]
	IPH[c]	0.65 (0.33-1.25)	0.43 (0.21-0.89)
	IVH[d]	2.41 (1.27-4.57)	2.03 (1.05-3.92)
Radiologic DCI (with or without clinical DCI)	TBV[a]	1.01 (1.00-1.03)[b]	1.02 (1.01-1.03)[b]
Clinical and radiologic DCI	TBV[a]	1.02 (1.00-1.03)[b]	1.02 (1.01-1.03)[b]

[a] Confounders: IPH and IVH.
[b] Per milliliter of blood.
[c] Confounders: WFNS, blood volume, and IVH.
[d] Confounder: blood volume.

DISCUSSION

In this study, a higher TBV, quantified with a fully automated method, was significantly associated with the development of DCI. The presence of an intraventricular hematoma was also positively associated with the development of DCI, whereas the presence of an intraparenchymal hematoma was negatively associated with DCI.

The association between TBV and DCI may appear small with an aOR of 1.02 per milliliter of blood. However, considering that the aOR is per milliliter of blood and that in our population, the mean TBV was 46.1 mL and the SD was almost 30 mL, this effect is substantial: A difference of 1 SD of TBV (30 mL) corresponds to an aOR of 1.81.

In both analyses assessing the association between TBV and DCI, we found similar aORs for all 3 outcome variables (clinical DCI, radiologic DCI, and both). This finding could justify using 1 outcome variable in future studies. Clinical DCI would be the most appropriate to use because almost all patients with radiologic DCI have clinical DCI. Moreover, the importance of radiologic DCI in the absence of clinical DCI is questionable. CT or MR imaging might be performed for other reasons, showing areas of ischemia that are clinically unnoticed.

In the first publication on the relation between the amount and distribution of subarachnoid blood detected on NCCT and cerebral vasospasm (detected on angiography), it was concluded that blood localized in the subarachnoid space in sufficient amounts at specific sites is the only important etiologic factor in vasospasm.[4] Because in our study we found an association of TBV, IPH, and IVH with clinical and radiologic DCI and not vasospasm, these studies are difficult to compare. One large difference is that in their study, not 1 patient with IVH developed clinical symptoms of DCI.

Only 1 more recent study investigated a semiautomatic blood quantification to assess the association between cisternal blood volume on NCCT and vasospasm after aSAH.[16] In this study, a positive association was found. However, the method used was laborious because all blood was outlined manually. Moreover, no correction for potential confounders was performed.

Our study results are in line with results from other studies showing that patients without intraventricular blood and with a small amount of cisternal blood after aSAH are less likely to develop DCI, though the results are somewhat different because these studies used vasospasm as an end point instead of DCI.[6,7] Nevertheless, these studies used the modified Fisher score instead of quantified blood volume to assess the amount of intracranial blood.[4]

The positive association between IVH and DCI is not yet understood. Blood can migrate toward the ventricles in 2 ways: first, straight from the aneurysm into the ventricles through a connecting hematoma or, second, by expansion of the subarachnoid blood toward one of the cisternal-ventricular foramina (Luschka, Magendie). The latter implies an initially higher volume of subarachnoid blood, with secondary ventricular redistribution. This might explain the association of IVH and DCI in this specific population. Additionally, patients who present with a nonaneurysmal IVH have a very low risk of developing DCI according to a study describing a series of patients with ruptured arteriovenous malformations, of whom 50 had an intraventricular component. Only 1 patient who also had an SAH component developed vasospasm, without signs of DCI.[17] According to these and our results, it seems that the combination of IVH and aSAH is worse than IVH or aSAH alone.

When one tries to explain the negative association of the presence of an IPH with clinical DCI, it could very well be that in these patients, clinical DCI was less often detected because they already had a neurologic deficit due to the IPH. To our knowledge, there is no literature confirming this theory. Further studies are needed to confirm this and to determine the association between IVH and IPH and DCI. In such a study, blood volume values for each separate compartment can be determined and subsequently associated with the clinical course.

The strengths of our study are fast and objective estimation of the TBV by using a validated automatic quantification method, adjustment for confounders to make the estimation of the association more reliable, and performance of a sensitivity analysis to evaluate the robustness of the model. In addition, we used DCI as an outcome variable instead of vasospasm because DCI is a more clinically relevant outcome measure and because vasospasm and DCI can occur independently.[2,12] In future studies, it might be possible to use the automated quantification method to study other subtypes of SAH (eg, due to intracranial dissection, AVM, benign perimesencephalic hemorrhage, and trauma).

Our study has some limitations. This was a retrospective study in which we could only study the data that were available in the clinical charts and on the available NCCTs. Because patients were followed up only during hospitalization, we may have potentially missed patients with DCI after discharge. In patients with clinical rebleeding within 24 hours after aSAH ictus, we might have underestimated the blood volume because this rebleeding was not CT-confirmed. Death during admission may be a competing risk for the development of DCI. Unfortunately, due to the composition of our data, we were unable to perform a reliable competing risk analysis.

Limitations of the automated quantification method are that imaging artifacts can make the results unreliable. Although we do not expect differences in the detection rate of TBV and aSAH between the anterior and posterior circulations, we have not yet investigated this possibility. Very small blood volumes with low density are not well-detected with automated detection.[10] The volume assessments were performed on relatively thick sections of 5 mm. Thinner sections could potentially increase accuracy. However, with thinner sections, the noise level increases as well, which may actually reduce the accuracy. The method was validated by using 5-mm sections, and 5 mm is the standard section thickness used in our hospital and the referring centers. The volume of the IPH and IVH and the blood volume in separate territories could not be separately delineated.

CONCLUSIONS

We show that a higher TBV, measured with our automated quantification method, is significantly associated with DCI. The results of this study encourage the use of rater-independent quantification methods in future multicenter studies on DCI prevention and prediction.

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3

Blood pressure and the risk of rebleeding and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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In preparation

ABSTRACT

Background and objective

Rebleeding and delayed cerebral ischemia (DCI) are major contributors to poor outcome after aneurysmal subarachnoid hemorrhage (aSAH). Blood pressure is presumed to be related to both complications and could therefore serve as a target for risk reduction. We aimed to assess the association between blood pressure and rebleeding and DCI in aSAH patients.

Methods

We performed an observational study in 1167 consecutive aSAH patients admitted to the intensive care unit (ICU) of two centers. We calculated adjusted hazard ratio's (aHR) for the association of blood pressure in the hours preceding rebleeding or DCI and these events. Based on the hypothesis of a non-linear effect of blood pressure on both outcome measures, the aHRs were presented graphically using restricted cubic splines, relative to a pre-chosen reference blood pressure of mean arterial pressure (MAP) of 100 mmHg and systolic blood pressure (sBP) of 150 mmHg.

Results

A MAP below 100 mmHg in the 6, 3 and 1 hours before rebleeding was statistically significantly associated with a decreased risk of rebleeding. For instance, for MAP 80 mmHg, the aHR was 0.30 (95%CI 0.11-0.80) within 6 hours, 0.27 (95%CI 0.10-0.72) with 3 hours, and 0.26 (95%CI 0.10-0.63) within 1 hour preceding rebleeding. A MAP of 60 mmHg or lower in the 24 hours before DCI was statistically significantly associated with an increased risk of DCI (MAP 60 mmHg: aHR 1.79 (95%CI 0.99-3.24), MAP 50 mmHg: aHR 2.59 (95%CI 1.12-5.96)).

Conclusions

Based on these observational data, MAP below 100 mmHg is associated with decreased risk of rebleeding, and a MAP of 60 mmHg or lower with increased risk of DCI. Whether lowering MAP below 100 mmHg will prevent rebleeding, or avoiding MAP of 60 mmHg or lower will prevent DCI should be further investigated in future randomized trials.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a subtype of stroke with high case fatality and morbidity. Two major contributors to poor outcome after aSAH are rebleeding[1-5] and delayed cerebral ischemia (DCI)[6,7]. These complications occur at different stages after the initial aSAH, with highest risk of recurrent bleeding in the first hours to days after the ictus, and the highest risk of DCI between the third and 14th day after ictus.[8]

Both complications seem to be associated with blood pressure, but previous reports have been inconsistent. The risk of rebleeding was found to be associated with high blood pressure in several studies[9-11], in particular with systolic blood pressures (sBP) higher than 150 mmHg[9] or 160 mmHg[10-12]. However, this association was not found in all studies, with one study actually observing sBP values within the normal range of 120 – 140 mmHg prior to rebleeding.[13] Data on blood pressure and DCI is also conflicting. DCI may occur more often in patients with a fall in blood pressure[14] and was associated with intra-operative hypotension in several studies[15-17]. However, this association between intra-operative hypotension and DCI was not found in another study[18].

As a result of the varying methods that were used in these studies, both in patient selection and in definition and analysis of blood pressure, it is currently not clear whether blood pressure is related to DCI or rebleeding. We aimed to assess the association between blood pressure in the hours preceding rebleeding and DCI and the occurrence of these events.

METHODS

Design and patients

This is an observational, multicenter cohort study. We retrieved data on all consecutive aSAH patients aged 18 years or older admitted to the intensive care unit (ICU) of two University Hospitals in The Netherlands: the University Medical Center Utrecht (UMCU) and the Amsterdam University Medical Center (AMC), from May 2003, through May 2011. The reason for not expanding this time period beyond 2011 was that from 2013, both centers participated in the ULTRA study in which patients were randomized to tranexamic acid or placebo in order to investigate the effectiveness of tranexamic acid in preventing rebleeding[19].

We defined an aSAH as either a subarachnoid hemorrhage (CT-proven or CT-negative with positive bilirubin in spinal fluid spectrophotometry performed more than 12 hours after the ictus) with a detected aneurysm or a subarachnoid hemorrhage with a definite

aneurysmal bleeding pattern in which the responsible aneurysm could not be verified despite CT-angiography or digital subtraction angiography. The reason to also include patients with a not immediately detected aneurysm is that these patients are also at risk of rebleeding or developing DCI.[20] Further, we included only those patients of whom blood pressure data was available during ICU admission.

Criteria for ICU admission were a Glasgow Coma Scale of 8 or lower necessitating intubation and mechanical ventilation, or hemodynamic or respiratory instability necessitating intensive care support. Further, patients could be admitted to the ICU after clipping of the symptomatic aneurysm. Patients not fulfilling admission criteria for the ICU were admitted to a dedicated neuro-medium care unit in both centers. From 2009, all aSAH patients presenting to the AMC were admitted to the ICU.

Procedures

During admission in the ICU, all patients were treated according to a standardized protocol that consisted of treatment with nimodipine administered orally 60 mg 6 times per day which was started immediately after hospital admission, cessation of antihypertensive medication on admission and intravenous administration of fluid aiming for normovolemia. In case the mean arterial pressure (MAP) dropped more than 20 mmHg due to administration of nimodipine, the administration was changed to 30 mg 12 times per day or cessation.

Blood pressure management in the ICU differed slightly between the participating centers. In the AMC, there were no strict upper limits to blood pressure prior to aneurysm occlusion until 2010, although sBP reaching 200 mmHg was usually treated. From 2010, MAP was kept below 135 mmHg prior to aneurysm occlusion. After aneurysm occlusion, MAP was kept above 90 mmHg until 2010, and above 80 mmHg from 2010. In the UMCU, a protocol for blood pressure management was installed in 2008. From that moment, sBP was kept below 180 mmHg prior to aneurysm occlusion. After aneurysm occlusion, sBP was accepted until 220 mmHg and MAP until 130 mmHg. Further, MAP was kept above 80 mmHg.

Data collection

For all patients, we collected data on the following variables: age, gender, clinical condition on admission according to the World Federation of Neurosurgical Societies (WFNS) scale[21], symptomatic aneurysm location, modality and timing of aneurysm treatment, amount of extravasated blood on admission CT assessed with the Hijdra-score[22], occurrence of DCI and occurrence of rebleeding. Clinical condition at admission as assessed with the WFNS scale was dichotomized into good clinical condition (WFNS 1-3) and poor clinical

condition (WFNS 4-5). The amount of extravasated blood as assessed with the Hijdra score was also dichotomized at the median for both cisternal (sumscore range 0–30) and ventricular (sumscore range 0–12) blood and added to a total Hijdra sum score.

For analysis on rebleeding, we decided beforehand to use both the MAP and sBP. For analysis on DCI, we decided beforehand to use the MAP as independent variable, as MAP is directly related to cerebral perfusion pressure (CPP) which is an important factor in maintaining adequate cerebral perfusion.[23] In both ICUs, intra-arterial blood pressures were measured continuously and stored in the electronic data servers at the ICUs. From these continuous measurements, only the hourly, nurse-validated blood pressures were extracted for statistical analyses. Since these validated measures can still be inaccurate based on typographical error, outliers were manually removed blinded for outcome measures. This did not result in the exclusion of patients.

Endpoints

The primary outcome measures were rebleeding and DCI during ICU admission. All events of rebleeding and DCI during hospital admission were assessed, but as blood pressure was only extracted during ICU admission and we were interested in the direct relation between blood pressure and the outcome measures, only the events during ICU admission were used in the analyses. Rebleeding was defined as either definite (CT-proven) or probable (defined as an acute clinical deterioration suspected for rebleeding by the treating physician) rebleeding. For the statistical analyses, both definite and probable rebleeding were combined. DCI was defined as a new clinical deterioration which could not be explained by other causes than DCI, following previously described consensus criteria.[24] The timing of rebleeding and DCI was estimated based on patients' records and the time of the CT scan performed to rule out other possible causes of the neurological deterioration. Both outcomes were assessed without prior knowledge of the blood pressure during ICU admission.

Ethics

The ethical review board of the AMC and UMCU approved of the study protocol and waived the need for informed consent (W11_091#11.17.0895 and 13-137/C).

Statistical analyses

Cox univariable and multivariable proportional hazard analysis with MAP or sBP as time dependent covariate was used to calculate hazard ratios (HR) for DCI and rebleeding with corresponding 95% confidence intervals (CI). Adjustments were made for the following a priori selected possible confounders: age, sex, clinical condition on admission (WFNS-

score), aneurysm treatment modality (clipping versus endovascular treatment), treatment center, amount of extravasated blood on admission CT (total Hijdra sumscore) and, for analyses on DCI only, rebleeding (prior to development of DCI, time dependent variable).

In the main analysis, we investigated the association between blood pressure in the hours preceding the event (rebleeding or DCI), and the occurrence of this event. For rebleeding, we hypothesized that the association between blood pressure and rebleeding would be based on high blood pressures and that this would be a more acute association. Therefore, we assessed the association between every increase in mmHg from the highest measured MAP and sBP within 1, 3 and 6 hours preceding rebleeding, and the occurrence of this event. In order to avoid a self-fulfilling prophecy by including increased blood pressure values actually caused by the rebleeding, we forwarded the timing of the rebleeding in all patients by one hour. For DCI, we hypothesized that the association between blood pressure and DCI would be based on low blood pressures and that this would be a more gradual association.[25,26] Therefore, we assessed the association between every increase in mmHg from the lowest measured MAP within 12 and 24 hours preceding DCI and the occurrence of this event.

We also hypothesized that the effect of blood pressure variables on the risk of rebleeding or DCI was not the same over the whole range of blood pressures, and was therefore non-linear. The results were thus presented graphically using restricted cubic splines. From these splines, we assessed the aHR for both outcome events per preceding blood pressure. For rebleeding, this was performed for MAP and sBP in the 6, 3 and 1 hours preceding rebleeding, with the reference MAP set at 100 mmHg and the reference sBP set at 150 mmHg. For DCI, this was performed for MAP in the 24 and 12 hours preceding DCI with the reference MAP set at 100 mmHg.

Censoring is a key characteristic in survival analyses. Censoring is not a problem when it does not influence the relation under study (non-informative censoring). However, in our study, censoring might have been informative in certain situations. Patients who died during ICU admission because they were in a poor clinical condition might have been at increased risk for DCI, which would lead to informative censoring. Therefore, we added a sensitivity analysis to the main analysis for the possibility of informative censoring using two extreme scenarios: 1) all patients who were censored because they died in the ICU developed DCI/rebleeding; 2): all patients who were censored because they died in the ICU were immune for development of DCI/rebleeding.

As this study was not designed for prediction of rebleeding or DCI, adding competing event analyses was not deemed necessary.

RESULTS

During the study period, 1263 aSAH-patients were admitted to the ICUs of both centers. Of these patients, blood pressure data were not available for 96 patients (8%), leaving 1167 aSAH-patients (AMC n=500 and UMCU n=667) included in the study.

The characteristics of the patients are shown in table 1. The mean age of the patients was 56 years (standard deviation 12.7) and 804 (69%) were female. Median time from ictus to rebleeding was 2 days (IQR 1 – 4.5) and to DCI 4 days (IQR 2.75 – 7). Median time between ictus and ICU admission was 1 day (interquartile range (IQR) 0 – 2), with 908 (78%) patients being admitted to the ICU ≤ 48 hours after ictus. Median length of stay in the ICU was 2 days (IQR 0 – 6). Patients in the AMC were more often coiled as compared to patients in the UMCU. Patients in the AMC had larger amounts of blood on their initial CT scan. The proportion of patients developing rebleeding or DCI was the same in both study centers.

Table 2 shows the baseline characteristics for patients who did or did not develop rebleeding or DCI. Patients who developed rebleeding more often had a poor WFNS score on admission, had larger amounts of blood on their initial CT scan, were more often not treated for their aneurysm, and more often had an aneurysm in the anterior circulation or an aneurysm that was not found. Patients who developed DCI more often had a poor WFNS score on admission, larger amounts of blood on the initial CT scan and were more often treated with an endovascular procedure as compared to patients who did not develop DCI in the ICU.

The primary outcome of rebleeding and DCI during ICU admission was known for all patients. Rebleeding occurred in 45 (4%) patients (36 definite, 9 probable). DCI occurred in 110 (9%) patients.

The distributions of MAP and sBP in the first 48 hours of ICU admission are shown in figure 1. As can be seen from these box plots, mean MAP was around 95 mmHg, with distributions ranging from 50 to 140 mmHg, with outliers around 150 mmHg. Mean sBP was around 150 mmHg, with distributions ranging from 70 to 230 mmHg, and outliers around 250 mmHg.

Rebleeding

A MAP below 100 mmHg in the 6, 3 and 1 hours before rebleeding was statistically significantly associated with a decreased risk of rebleeding. The spline curves and aHRs for MAP with corresponding 95% CI are shown in figure 2a. MAP values above 100 mmHg were not associated with rebleeding. No association was found between sBP values within 6, 3 and 1 hour preceding rebleeding and rebleeding. The spline curves and aHRs for sBP with corresponding 95% CI are shown in figure 2b.

Table 1. Baseline characteristics.

	Entire study population n=1167	AMC n=500	UMC n=667
Age in years (mean, SD)	56 (12.7)	55 (13)	57 (13)
Female (%)	804 (69)	343 (69)	461 (69)
Hypertension[a]	311 (27)	121 (24)	189 (28)
Antihypertensive drugs[b]	264 (23)	98 (20)	165 (25)
WFNS score > 3	567 (49)	256 (51)	311 (47)
Aneurysm treatment			
Coil (%)	446 (38)	302 (60)	144 (22)
Clip (%)	453 (39)	108 (22)	345 (52)
Other (%)	7 (0,5)	1 (0)	6 (1)
No treatment (%)	261 (22)	89 (18)	166 (25)
No aneurysm found (%)	46 (4)	17 (3)	29 (4)
Rebleeding (%)[c]	211 (18)	86 (18)	125 (19)
In the ICU (%)	45 (4)[#]	18 (4)	27 (4)
DCI (%)	255 (22)	136 (27)	119 (18)
In the ICU (%)	110 (9%)	52 (10)	58 (9)
Aneurysm location			
Anterior circulation (%)	780 (67)	323 (65)	457 (69)
Posterior circulation (%)	318 (27%)	142 (28)	176 (26)
Not found (%)	69 (6)	35 (7)	34 (5)
Hijdra scores[d]			
Sum score cisterns > median 24 (%)	527 (45)	256 (55)	271 (42)
Sum score ventricles > median 2 (%)	533 (46)	226 (49)	307 (48)
Total sum score > median 26 (%)	568 (49)	270 (58)	298 (46)
ICH present[e]	290 (25)	137 (29)	153 (24)
Length of ICU stay (days) median [IQR]	2 [0 – 6]	2 [1 – 6]	2 [1 – 6]
Time ictus to rebleeding in the ICU (days) median [IQR]	2 [1 – 4.5]	1 [1 – 3.5]	2 [1 – 8]
Time ictus to DCI in the ICU (days) median [IQR]	4 [2.75 – 7]	4 [2 – 6.75]	6 [3 – 9]

AMC Amsterdam University Medical Center, *UMCU* University Medical Center Utrecht, *WFNS* World Federation of Neurosurgical Societies, *ICU* intensive care unit, *DCI* delayed cerebral ischemia, *ICH*, intracerebral hematoma; *IQR* interquartile range.

[a] 38 missing; [b] 79 missing; [c] 10 missing; [d] 55 missing; [e] 47 missing

[#] in 6 patients rebleeding occurred after coiling, in 2 patients rebleeding occurred after clipping

Table 2. Baseline characteristics in patients who did or did not develop rebleeding or DCI.

	No rebleeding n=1112	Rebleeding n=45	No DCI n = 1057	DCI n = 110
Number of patients per center				
AMC (%)	472 (42)	18 (40)	448 (42)	52 (47)
UMCU (%)	640 (58)	27 (60)	609 (58)	58 (53)
Age in years (mean, SD)	56 (12.6)	57 (12.8)	56 (12.8)	56 (11.7)
Female (%)	771 (69)	25 (56)	734 (69)	70 (64)
Hypertension[a]	297 (27)	14 (31)	278 (26)	33 (30)
Antihypertensive drugs[b]	252 (23)	12 (27)	236 (22)	28 (25)
WFNS score > 3	524 (47)	38 (84)	496 (47)	71 (65)
Aneurysm treatment				
Coil (%)	429 (39)	12 (27)[#]	381 (36)	65 (59)
Clip (%)	448 (40)	4 (9)[##]	419 (40)	34 (31)
Other endovascular (%)	7 (1)	-	5 (0.5)	2 (2)
No treatment (%)	228 (21)	29 (64)	252 (24)	9 (8)
Rebleeding both in- and outside the ICU (%)[c]			190 (18)	21 (19)
Aneurysm location				
Anterior circulation (%)	754 (68)	19 (42)	707 (67)	73 (66)
Posterior circulation (%)	301 (27)	16 (36)	283 (27)	35 (32)
Not found (%)	57 (5)	10 (22)	67 (6)	2 (2)
Hijdra scores[d]				
Sum score cisterns > median 24 (%)	494 (44)	27 (60)	461 (44)	66 (60)
Sum score ventricles > median 2 (%)	501 (45)	30 (67)	469 (44)	64 (58)
Total sum score > median 26 (%)	533 (48)	29 (64)	499 (47)	69 (63)
ICH present[e]	280 (25)	10 (22)	263 (25)	27 (25)
Length of ICU stay (days) median [IQR]	2 [1 – 6]	4 [2 – 9]	2 [1 – 4]	10 [6 – 15.3]
Time ictus to rebleeding (days) median [IQR]	-	2 [1 – 4.5]	-	-
Time ictus to DCI (days) median [IQR]	-	-	-	4 [2.75 – 7]

DCI delayed cerebral ischemia, *AMC* Amsterdam University Medical Center, *UMCU* University Medical Center Utrecht, *WFNS* World Federation of Neurosurgical Societies, *ICH* intracerebral hematoma, *ICU*, intensive care unit, *IQR,* interquartile range.

[a] 38 missing; [b] 9 missing; [c] 10 missing; [d] 55 missing; [e] 47 missing

[#] in 6 patients rebleeding occurred after coiling, [##] in 2 patients rebleeding occurred after clipping

DCI

A MAP of 60 mmHg or lower in the 24 hours before DCI was statistically significantly associated with an increased risk of DCI. No association was found between MAP values in the 12 hours preceding DCI and DCI. The spline curves and aHRs with corresponding 95% CI are shown in figure 3.

Sensitivity analyses

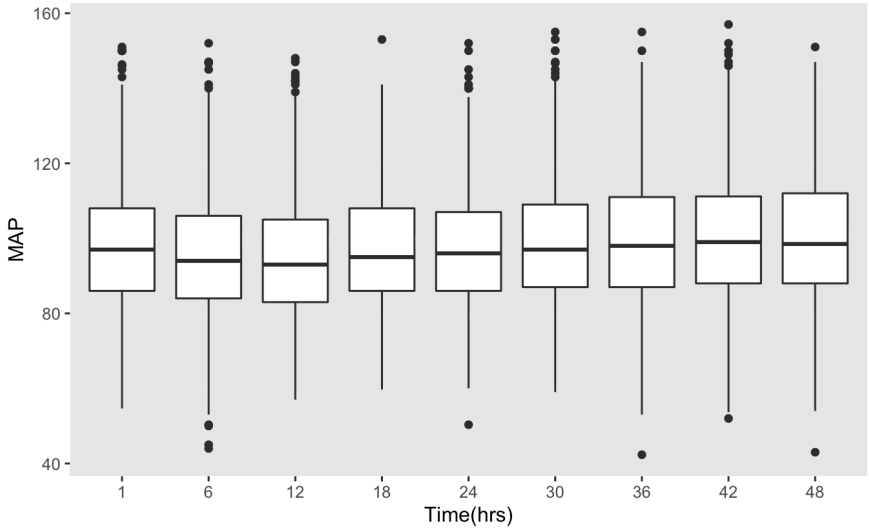
For rebleeding, the number of events increased to 213 with extreme scenario 1 and decreased to 44 with extreme scenario 2. For DCI, the number of events increased to 298 with extreme scenario 1 and decreased to 105 with extreme scenario 2. The results of the sensitivity analyses are shown in the supplementary material. A summary of the results is described in the following section.

For rebleeding, the direction of the effect for MAP and sBP and rebleeding changed with extreme scenario 1: a MAP below 100 mmHg and a sBP below 150 mmHg in the 6, 3 and 1 hours preceding rebleeding were both statistically significantly associated with an increased risk of rebleeding. Further, a sBP of 160, 170 and 180 mmHg was statistically significantly associated with a decreased risk of rebleeding in the 6 and 3 hours preceding rebleeding and a sBP of 160 was statistically significantly associated with a decreased risk of rebleeding in the 1 hour preceding rebleeding. With extreme scenario 2, both the direction and the magnitude of the effect for MAP and sBP and rebleeding were unchanged compared to the main analyses.

For DCI, the direction of the effect for MAP and DCI remained unchanged but the magnitude of the effect increased with extreme scenario 1: a MAP of 70 mmHg and lower was statistically significantly associated with increased risk of DCI, both within 24 and 12 hours preceding DCI. With extreme scenario 2, the direction of the effect for MAP and DCI changed, but was never statistically significantly associated with the risk of DCI.

Figure 1. Distribution of blood pressure in the first 48 hours of ICU admission.

a. Mean arterial pressure (MAP)



b. Systolic blood pressure (sBP)

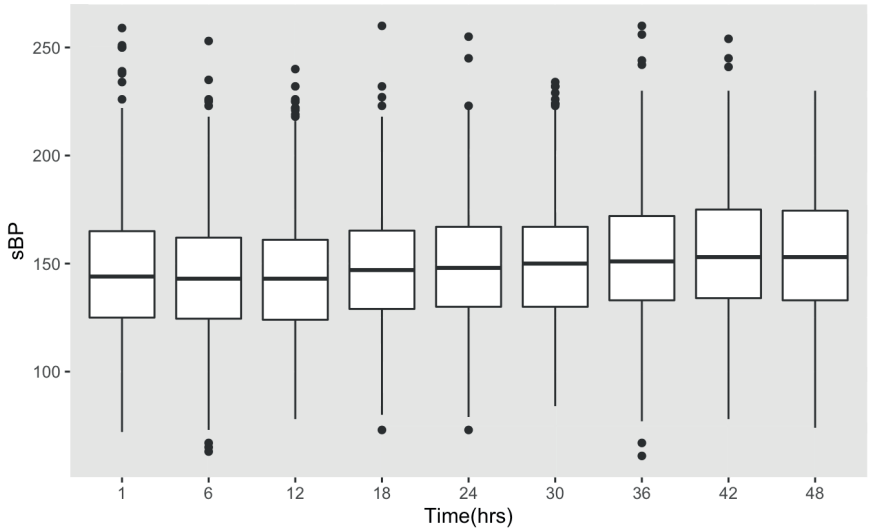
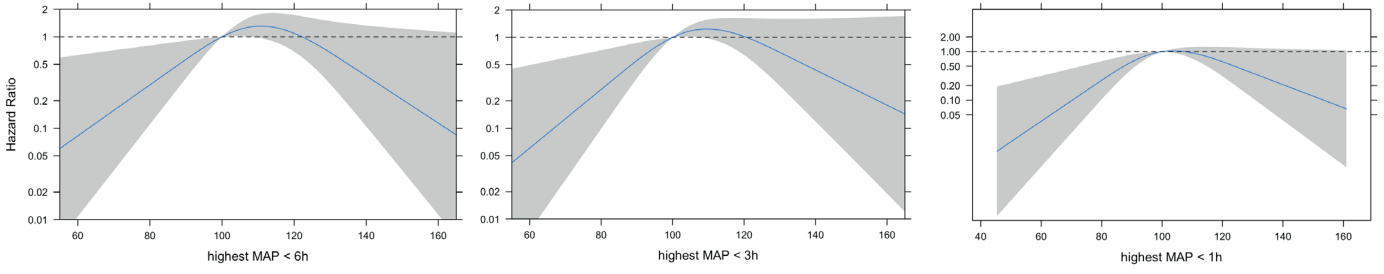


Figure 2. Risk of rebleeding per blood pressure value in the 6, 3 and 1 hours preceding rebleeding.

2a. MAP

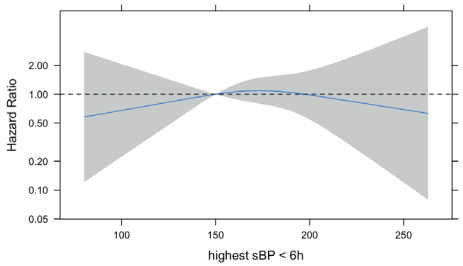


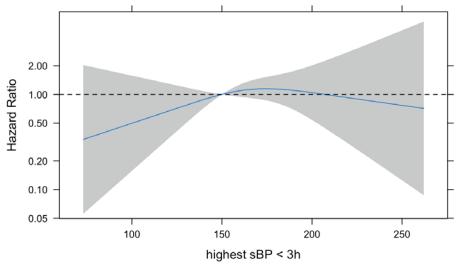
Highest MAP < 6 h (mmHg)	aHR	95% CI
60	0.08	0.01 – 0.63
70	0.16	0.03 – 0.71
80	0.30	0.11 – 0.80
120	1.09	0.69 – 1.73
130	0.67	0.30 – 1.49
140	0.37	0.10 – 1.33
150	0.21	0.03 – 1.23
160	0.11	0.01 – 1.14

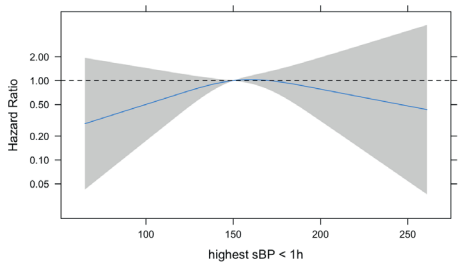
Highest MAP < 3 h (mmHg)	aHR	95% CI
60	0.06	0.01 – 0.49
70	0.13	0.03 – 0.60
80	0.27	0.10 – 0.72
120	1.02	0.64 – 1.63
130	0.68	0.29 – 1.60
140	0.44	0.12 – 1.61
150	0.28	0.05 – 1.64
160	0.18	0.02 – 1.69

Highest MAP < 1 h (mmHg)	aHR	95% CI
60	0.04	0.00 – 0.32
70	0.10	0.02 – 0.45
80	0.26	0.10 – 0.63
120	0.62	0.31 – 1.23
130	0.36	0.11 – 1.18
140	0.21	0.04 – 1.14
150	0.12	0.01 – 1.10
160	0.07	0.00 – 1.06

2b. sBP







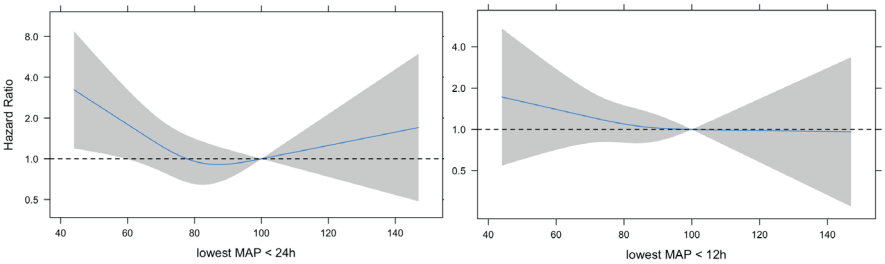
Highest sBP < 6 h (mmHg)	aHR	95% CI
120	0.79	0.41 – 1.54
130	0.86	0.56 – 1.33
140	0.93	0.75 – 1.15
160	1.06	0.89 – 1.25
170	1.09	0.82 – 1.45
180	1.08	0.76 – 1.54

Highest sBP < 3 h (mmHg)	aHR	95% CI
120	0.67	0.34 – 1.30
130	0.77	0.50 – 1.18
140	0.88	0.72 – 1.08
160	1.09	0.94 – 1.27
170	1.14	0.90 – 1.46
180	1.14	0.82 – 1.59

Highest sBP < 1 h (mmHg)	aHR	95% CI
120	0.69	0.39 – 1.22
130	0.81	0.57 – 1.13
140	0.92	0.79 – 1.06
160	1.03	0.92 – 1.16
170	1.00	0.78 – 1.30
180	0.94	0.60 – 1.47

MAP mean arterial pressure, *sBP* systolic blood pressure

Figure 3. Risk of DCI per MAP value in the 24 hours preceding DCI.



Lowest MAP < 24 h (mmHg)	aHR	95% CI
50	2.59	1.12 – 5.96
60	1.79	0.99 – 3.24
70	1.25	0.81 – 1.93

Lowest MAP < 12 h (mmHg)	aHR	95% CI
50	1.59	0.61 – 4.20
60	1.40	0.71 – 2.76
70	1.23	0.80 – 1.90

MAP mean arterial pressure, *DCI* delayed cerebral ischemia

DISCUSSION

In summary, we found a statistically significant association between MAP values lower than 100 mmHg in the 6, 3 and 1 hours preceding rebleeding and decreased risk of rebleeding and a statistically significant association between MAP values of 60 mmHg or lower in the 24 hours preceding DCI and increased risk of DCI.

In our study, we found no association between high blood pressure and the occurrence of rebleeding, neither for MAP nor for sBP. With previous studies showing conflicting results (some finding an association between high sBP values and rebleeding [9,10-12,27], and others not[28,29]), it remains unclear whether high (and which) blood pressure values are associated with increased risk of rebleeding. An interesting finding in our study however, was that lower MAP values were associated with decreased risk of rebleeding, a finding that could serve as a potential target for preventing rebleeding when confirmed in future prospective studies.

Concerning DCI, the association between impaired cerebral autoregulation and DCI is well established.[30-37] However, the association between blood pressure and DCI is not. In one study, a drop in sBP was seen more often in patients who developed clinical signs of DCI as compared to those who did not[14] and treating hypertension resulted in increased risk of DCI[38,39]. However, in another study, MAP in the three days before DCI was actually higher in patients who developed DCI as compared to those who did not.[40] Intraoperative hypotension was associated with vasospasm[17] or clinical and radiological DCI[16] in some studies, and a recent small matched case-control study suggested that DCI could be prevented by keeping intraoperative sBP above 95 mmHg, diastolic blood pressure above 50 mmHg and MAP above 62 mmHg[41]. However, intraoperative hypotension was found not associated with DCI in another study[18], and a recent large observational study of 1099 patients showed no association between intraoperative hypotension and poor outcome after aSAH.[42] The association we found between MAP of 60 mmHg or lower and an increased risk of DCI is therefore difficult to compare to these previous conflicting results, and is further complicated by the varying definitions of blood pressure and varying statistical analyses that were used. It is plausible however that a MAP of 60 or lower would increase the risk of DCI, as maintaining a constant cerebral blood flow through cerebral autoregulation becomes impaired with MAP below 60 mm Hg.[43,44] Our results need to be confirmed in future prospective studies.

With the sensitivity analyses, several changes in the association between blood pressure and the outcome events were seen. This was only the case for extreme scenario 1, probably due to the fact that the number of outcome events (rebleeding or DCI) increased substantially when all patients who had died during ICU admission were added.

For rebleeding, the direction and the magnitude of the association between MAP and sBP and rebleeding changed, with lower MAP values now being statistically significantly associated with an increased risk of rebleeding. However, it seems unlikely that all patients who died in the ICU (and who were thus added as an additional event of rebleeding to this sensitivity analysis) actually also had suffered a rebleeding. Therefore it is more likely that we are observing the association between lower blood pressures and an increased risk of death. The same holds true for the increased association that was seen with this sensitivity analysis for low MAP values and the increased risk of DCI. Again it is more likely that we are observing the association between low blood pressure and risk of death.

Our study has several limitations. First of all, we included only aSAH patients who were admitted to the ICU. As blood pressures are kept within strict limits in the ICU, we were only able to assess the variation in blood pressure within these limits. This makes our results less generalizable to an aSAH population not admitted to the ICU.

Also, we had no information on blood pressure levels prior to ICU admission. Especially for patients who developed rebleeding or DCI shortly after ICU admission, these blood pressure levels might have been important for assessing the association between blood pressure and the outcome event.

Another possible limitation is the rather old dataset that was used, which might result in less generalizability of the results to the current time. On the one hand, in the first years of the study period, there were no strict limits for high blood pressure which might have resulted in an actual increased possibility of finding an association between high blood pressure and rebleeding. On the other hand, in the first years of the study, MAP was kept above 90 mmHg in the AMC, which might have resulted in a decreased possibility of finding an association between low blood pressure and DCI. Most importantly however, the presence or absence of an association between blood pressure and rebleeding or DCI will not change in time, and therefore we feel that the rather old dataset will not have influenced results majorly.

We excluded 96 patients because of missing blood pressure data. However, as this was only a small proportion of all patients and the occurrence of rebleeding or DCI occurs independent of the availability of blood pressures, we do not feel that this has had major impact on the results.

There were some baseline differences between the two centers. However, the proportion of patients developing rebleeding or DCI did not differ. By adding treatment center as a variable to adjust for in our analyses, we have tried to take these in-between center differences into account.

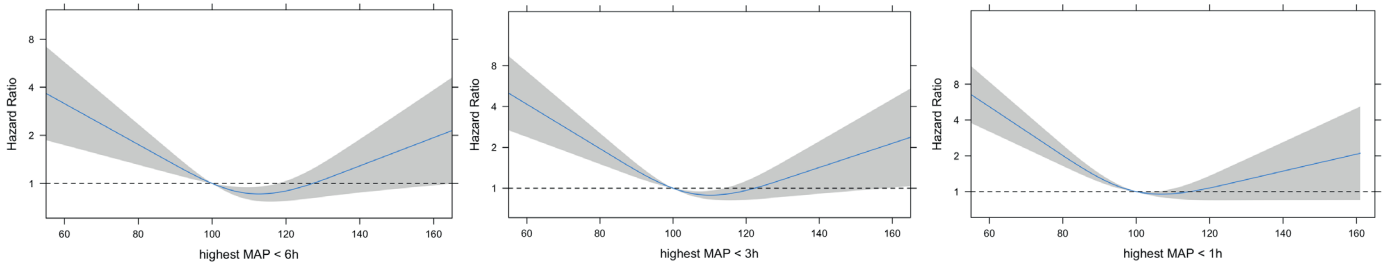
The most important strength of this study is that we were able to assess the time-dependent relation between blood pressure and rebleeding or DCI in a precise way, as we were able to collect extensive data on blood pressures in an hourly fashion and could accurately time all the events of DCI and rebleeding.

CONCLUSIONS

Based on these observational data, MAP below 100 mmHg is associated with decreased risk of rebleeding, and a MAP of 60 mmHg or lower with increased risk of DCI. Whether lowering MAP below 100 mmHg will prevent rebleeding, or avoiding MAP of 60 mmHg or lower will prevent DCI should be further investigated in future randomized trials.

SUPPLEMENTARY MATERIAL – SENSITIVITY ANALYSES

Figure 1. Risk of rebleeding per blood pressure value in the 6, 3 and 1 hours preceding rebleeding.
1a. Extreme scenario 1*
MAP

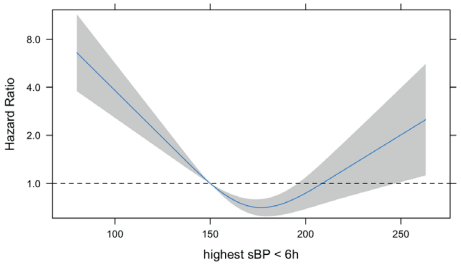


Highest MAP < 6 h (mmHg)	aHR	95% CI
60	3.16	1.74 – 5.74
70	2.35	1.51 – 3.67
80	1.75	1.31 – 2.35
120	0.90	0.78 – 1.04
130	1.05	0.82 – 1.34
140	1.29	0.88 – 1.89
150	1.58	0.93 – 2.69
160	1.93	0.97 – 3.85

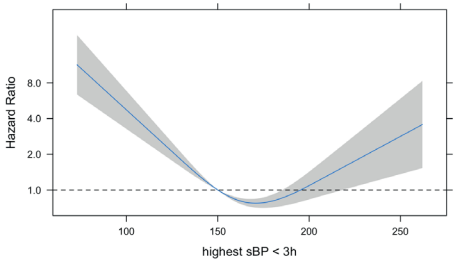
Highest MAP < 3 h (mmHg)	aHR	95% CI
60	4.16	2.39 – 7.26
70	2.86	1.90 – 4.30
80	1.96	1.51 – 2.55
120	0.96	0.82 – 1.13
130	1.16	0.86 – 1.56
140	1.42	0.91 – 2.22
150	1.75	0.96 – 3.17
160	2.14	1.01 – 4.54

Highest MAP < 1 h (mmHg)	aHR	95% CI
60	5.16	3.20 – 8.34
70	3.22	2.29 – 4.53
80	2.01	1.64 – 2.46
120	1.07	0.85 – 1.36
130	1.36	0.85 – 1.88
140	1.49	0.85 – 2.60
150	1.75	0.85 – 3.61
160	2.07	0.85 – 5.01

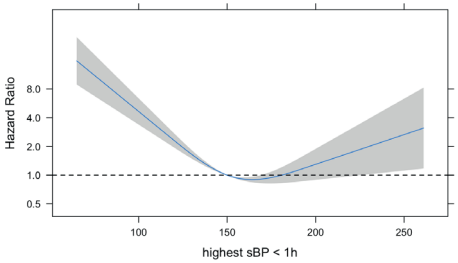
sBP



Highest sBP < 6 h (mmHg)	aHR	95% CI
120	2.21	1.75 – 2.80
130	1.69	1.45 – 1.97
140	1.29	1.19 – 1.39
160	0.82	0.77 – 0.87
170	0.72	0.65 – 0.80
180	0.71	0.62 – 0.81



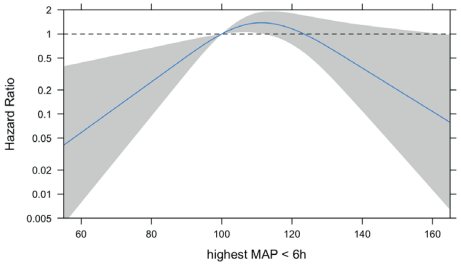
Highest sBP < 3 h (mmHg)	aHR	95% CI
120	2.47	2.00 – 3.07
130	1.79	1.56 – 2.05
140	1.31	1.23 – 1.39
160	0.83	0.79 – 0.87
170	0.77	0.71 – 0.84
180	0.81	0.71 – 0.91

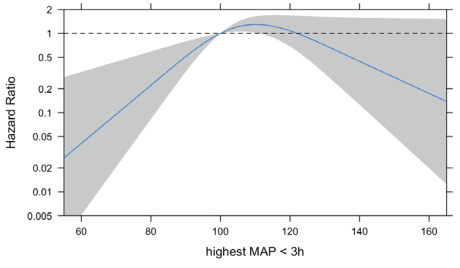


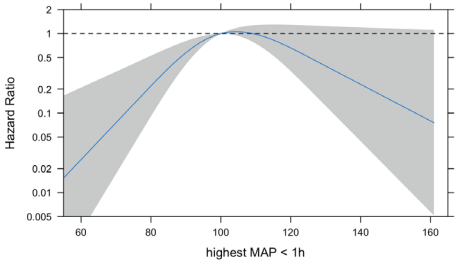
Highest sBP < 1 h (mmHg)	aHR	95% CI
120	2.31	1.95 – 2.75
130	1.65	1.49 – 1.83
140	1.23	1.18 – 1.29
160	0.91	0.87 – 0.95
170	0.91	0.82 – 1.01
180	0.99	0.82 – 1.19

1b. Extreme scenario 2**

MAP





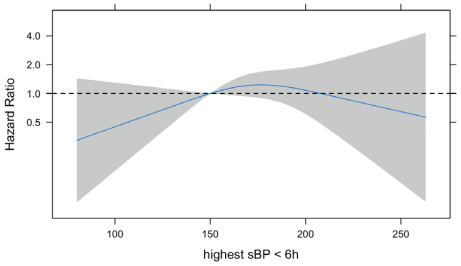


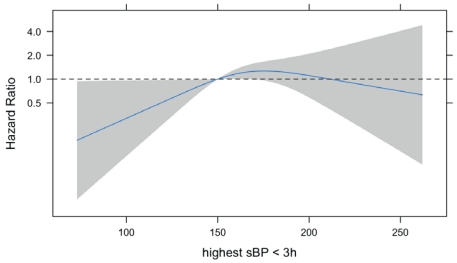
Highest MAP < 6 h (mmHg)	aHR	95% CI
60	0.06	0.01 – 0.44
70	0.12	0.03 – 0.54
80	0.25	0.09 – 0.67
120	1.16	0.74 – 1.82
130	0.70	0.32 – 1.51
140	0.38	0.11 -1.30
150	0.20	0.04 – 1.15
160	0.11	0.01 – 1.03

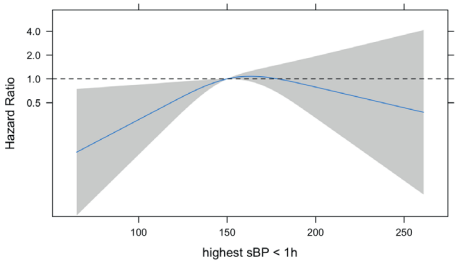
Highest MAP < 3 h (mmHg)	aHR	95% CI
60	0.04	0.01 – 0.33
70	0.10	0.02 – 0.44
80	0.22	0.08 – 0.59
120	1.08	0.68 – 1.70
130	0.71	0.31 – 1.61
140	0.44	0.13 – 1.57
150	0.28	0.05 – 1.55
160	0.17	0.02 – 1.53

Highest MAP < 1 h (mmHg)	aHR	95% CI
60	0.03	0.00 – 0.21
70	0.08	0.02 – 0.33
80	0.22	0.09 – 0.53
120	0.66	0.34 – 1.29
130	0.39	0.12 – 1.24
140	0.23	0.04 – 1.19
150	0.14	0.02 – 1.15
160	0.08	0.01 – 1.12

sBP







Highest sBP < 6 h (mmHg)	aHR	95% CI
120	0.62	0.33 – 1.17
130	0.73	0.48 – 1.11
140	0.86	0.70 – 1.05
160	1.13	0.96 – 1.33
170	1.21	0.92 – 1.59
180	1.22	0.87 – 1.72

Highest sBP < 3 h (mmHg)	aHR	95% CI
120	0.51	0.27 – 0.97
130	0.65	0.43 – 0.98
140	0.82	0.68 – 0.99
160	1.16	1.01 – 1.34
170	1.25	0.99 – 1.58
180	1.26	0.91 – 1.73

Highest sBP < 1 h (mmHg)	aHR	95% CI
120	0.53	0.30 – 0.91
130	0.68	0.49 – 0.95
140	0.85	0.74 – 0.98
160	1.07	0.96 – 1.20
170	1.06	0.83 – 1.36
180	0.99	0.64 – 1.53

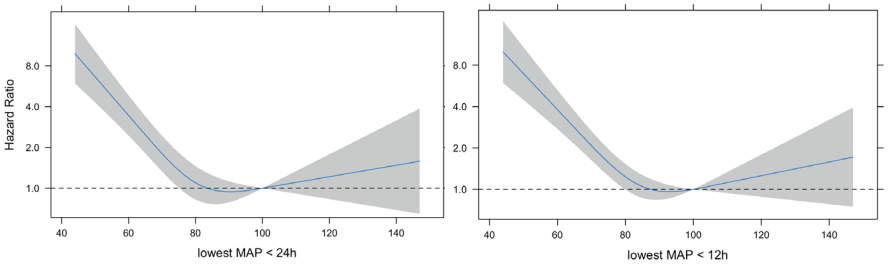
MAP mean arterial pressure, *sBP* systolic blood pressure

* Extreme scenario 1: all patients who were censored because they died in the ICU developed rebleeding

** Extreme scenario 2: all patients who were censored because they died in the ICU were immune for development of rebleeding

Figure 2. Risk of DCI per MAP value in the 24 and 12 hours preceding DCI.

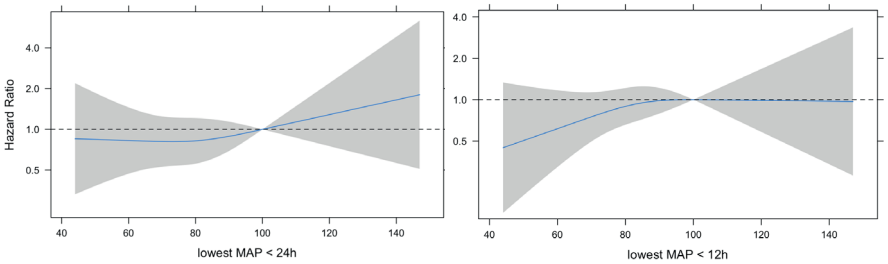
2a. Extreme scenario 1



Lowest MAP < 24 h (mmHg)	aHR	95% CI
50	6.63	4.30 – 10.25
60	3.44	2.44 – 4.85
70	1.80	1.33 – 2.43

Lowest MAP < 12 h (mmHg)	aHR	95% CI
50	6.95	4.47 – 10.81
60	3.80	2.75 – 5.26
70	2.08	1.63 – 2.66

2b. Extreme scenario 2



Lowest MAP < 24 h (mmHg)	aHR	95% CI
50	0.84	0.38 – 1.86
60	0.83	0.47 – 1.45
70	0.81	0.53 – 1.25

Lowest MAP < 12 h (mmHg)	aHR	95% CI
50	0.50	0.20 – 1.26
60	0.61	0.32 – 1.17
70	0.75	0.50 – 1.13

MAP mean arterial pressure, *sBP* systolic blood pressure

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4

Preventive antibiotics and delayed cerebral ischaemia in patients with aneurysmal subarachnoid haemorrhage admitted to the intensive care unit

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ABSTRACT

Introduction

Delayed cerebral ischemia (DCI) is an important contributor to poor outcome after aneurysmal subarachnoid haemorrhage (aSAH). Development of DCI is multifactorial, and inflammation, with or without infection, is one of the factors independently associated with development of DCI and poor outcome. We thus postulated that preventive antibiotics might be associated with a reduced risk of DCI and subsequent poor outcome in aSAH patients.

Methods

We performed a retrospective cohort-study in intensive care units (ICU) of three university hospitals in The Netherlands. We included consecutive aSAH patients with minimal ICU stay of 72 h who received either preventive antibiotics (SDD: selective digestive tract decontamination including systemic cefotaxime or SOD: selective oropharyngeal decontamination) or no preventive antibiotics. DCI was defined as a new hypodensity on CT with no other explanation than DCI. Hazard ratio's (HR) for DCI and risk ratio's (RR) for 28-day case-fatality and poor outcome at 3 months were calculated, with adjustment (aHR/aRR) for clinical condition on admission, recurrent bleeding, aneurysm treatment modality and treatment site.

Results

Of 459 included patients, 274 received preventive antibiotics (SOD or SDD) and 185 did not. With preventive antibiotics, the aHR for DCI was 1.0 (95 % CI 0.6–1.8), the aRR for 28-day case-fatality was 1.1 (95 % CI 0.7–1.9) and the aRR for poor functional outcome 1.2 (95 % CI 1.0–1.4).

Conclusions

Preventive antibiotics were not associated with reduced risk of DCI or poor outcome in aSAH patients in the ICU.

INTRODUCTION

Delayed cerebral ischaemia (DCI) is a major complication after aneurysmal subarachnoid haemorrhage (aSAH) and an important contributor to poor outcome.[1] The cause of DCI is multifactorial[2] with one of the postulated underlying mechanisms being the presence of an inflammatory response[3,4]. Infections are seen in up to 30–40% of patients with aSAH during hospitalisation[5] and signs of systemic inflammation, with or without the presence of an infection, are independent predictors of DCI and poor functional outcome after aSAH[6-10].

Selective digestive tract decontamination (SDD; consisting of 4 days of intravenous cefotaxime plus topical application of tobramycin, colistin and amphotericin-B in oropharynx and stomach) and selective oropharyngeal decontamination (SOD; consisting of oropharyngeal application only) have been proven to reduce respiratory tract colonisation with Gram-negative bacteria and to improve 28-day survival in a mixed population of patients admitted to the intensive care unit (ICU).[11] We postulated that preventive antibiotics, through influencing infection or inflammation, are associated with a reduced risk of DCI and subsequently improved outcome in patients with aSAH admitted to the ICU.

MATERIALS AND METHODS

We retrieved data on aSAH patients aged C18 years, admitted to the ICU within 72 h after aSAH from three large university hospitals in The Netherlands: the University Medical Center Utrecht (UMCU); the Academic Medical Center Amsterdam (AMC); and the University Medical Center Groningen (UMCG) from May 2003 until May 2011. After 2011, preventive antibiotics (SOD or SDD), were considered standard care in all three participating centres. Aneurysmal SAH was defined as subarachnoid blood with an associated aneurysm found on CT-angiogram or digital subtraction angiography (DSA). However, we also included patients in whom no aneurysm was found during admission but who had a definite aneurysmal bleeding pattern since these patients are also at risk of developing DCI. The inclusion criterion within 72 h after the aSAH was used to minimize the risk that DCI had already occurred before ICU admittance.

Of the included patients, 73 participated in one of two controlled, cluster-randomised crossover studies in which SOD, SDD and no antibiotics[11] or SOD and SDD[12] were compared. In these studies, the treatment regime would only be assigned if the anticipated stay in the ICU was more than 72 h and/or expected duration of intubation was more than 48 h. Therefore, in order to equalize our inclusion criteria, all included patients outside these

study periods had to have an ICU length-of-stay of at least 72 h, irrespective of intubation status. Whether these patients were treated with SOD, SDD or no preventive antibiotics depended on the local protocol of the treatment centre at the time of admittance.

During admission, all patients were treated according to a standardised protocol that consisted of absolute bed rest until aneurysm treatment, oral doses of nimodipine, cessation of antihypertensive medication and intravenous administration of fluid with the aim of normovolaemia.

For all patients, we extracted the following variables: age, gender, clinical condition at admission according to the World Federation of Neurosurgical Societies (WFNS) scale[13], aneurysm location, modality of aneurysm treatment, amount of extravasated blood on admission CT as assessed with the Hijdra score[14], presence of an intracerebral haematoma (ICH), occurrence of DCI, occurrence of a recurrent bleeding, preventive antibiotics regime (SOD, SDD or no antibiotics), 28-day survival (the primary endpoint of the SDD studies) and functional outcome assessed with the modified Rankin Scale (mRS)[15] 3 months after aSAH. The clinical condition at time of admission assessed with the WFNS scale was dichotomised into good clinical condition (WFNS 1–3) and poor clinical condition (WFNS 4–5). The amount of extravasated blood as assessed with the Hijdra score was dichotomised at their median for both cisternal (sum score range 0–30) and ventricular (sum score range 0–12) blood. The two scores were added to a total Hijdra sum score which was in turn dichotomised at the added median scores for cisternal and ventricular blood.

The primary outcome measure was the occurrence of DCI defined as a new hypodensity on CT scan with no other explanation (e.g. edema or ischaemia from coiling or clipping) than DCI.[16] Secondary outcome measures were 28-day case-fatality and poor outcome after 3 months defined as a mRS score of 4, 5 or death.

Ethics

The ethical review board of the AMC approved the study protocol (reference number W14_151#14.17.0188).

Sample size calculation and statistical analyses

We calculated that a sample of 584 patients (292 per group) would yield a power of 80%, at a significance level of 0.05, to detect a 10% absolute difference (from 30 to 20%) in occurrence of DCI in the preventive antibiotics group versus the control group.

Cox univariable and multivariable regression analysis (for DCI) and Poisson univariable and multivariable regression analysis (for 28-day case -fatality and poor outcome at 3 months) were performed to calculate hazard ratios (HR) and risk ratios (RR) with corresponding 95% confidence intervals (CI). We primarily investigated the effect of preventive antibiotics combined (SOD or SDD) versus no antibiotics, but also investigated the effects of SOD and SDD alone. To identify which co-variables should be added to the multivariable analyses as important confounders (defined as variables that changed the crude HR or RR by more than 10%), we performed bivariable analyses with previously chosen co-variables known to be associated with occurrence of DCI or poor outcome (age, gender, clinical condition on admission (WFNS score), recurrent bleeding prior to DCI, aneurysm treatment modality, intracerebral haemorrhage, amount of subarachnoid blood (Hijdra score) and—for 28-day case-fatality and poor outcome—presence of DCI). With this analysis, the variables clinical condition on admission (WFNS score), recurrent bleeding and aneurysm treatment modality were identified and included in the multivariable analyses.

Since patients were derived from three different sites, we investigated whether all patients could be analysed together by adding an interaction term between preventive antibiotics regime and treatment site to the uni- and multivariable analyses. Interaction terms appeared not to be statistically significant, and thus we concluded it was justified to analyse all patients together. To adjust for other possible between-centre differences, we did add the variable treatment site to the multivariable analyses.

We added two sensitivity analyses. First, 61 patients had died or had been discharged to another hospital within 10 days without having had follow-up imaging. In the primary analysis, these patients were scored as having no DCI, but we added a sensitivity analysis in which they were all scored as having DCI. Further, 28 patients were transferred to another hospital and were lost to follow-up for the outcome of 28-day case-fatality. In the primary analysis, we excluded these patients, but we added a sensitivity analysis in which we assumed that these patients were alive at 28 days after aSAH.

RESULTS

Of the 459 aSAH patients who fulfilled the inclusion criteria, 274 received preventive antibiotics (61 SOD, 213 SDD) and 185 did not. Seventy-three patients (16%) were derived from one of the two SDD studies; the remaining patients originated from cohorts of patients in between or after the two studies. The mean age of the patients was 57 years and 322 (70%) were female. Four hundred and eleven patients (90%) were admitted to the ICU within 24 h after the haemorrhage and DCI had not yet occurred in any of the patients before admittance to the ICU.

Demographics and baseline characteristics are shown in Table 1. Compared with the group of patients not receiving preventive antibiotics, those in the antibiotics group were more often coiled (56 vs. 44%,), less often clipped (30 vs.40 %), and more often had a WFNS score >3 at admission (71 vs. 53%), or an intracerebral haematoma (35 vs. 25%).

Table 1. Baseline characteristics.

	Preventive antibiotics (SOD/SDD) n = 274	**No preventive antibiotics n = 185**
Number of patients per centre		
AMC (%)	158 (58)	25 (14)
UMCU (%)	102 (37)	27 (15)
UMCG (%)	14 (5)	133 (72)
Mean age, years (range)	57 (24 – 84)	57 (25 – 84)
Female (%)	186 (68)	136 (74)
WFNS score > 3	194 (71)	98 (53)
Aneurysm treatment		
Coil (%)	154 (56)	82 (44)
Clip (%)	81 (30)	73 (40)
Stenting (%)	0	1 (1)
No treatment (%)	39 (14)	29 (16)
Recurrent bleeding (%)	67 (25)	38 (21)
Radiological parameters		
Aneurysm location		
Anterior circulation (%)	179 (65)	122 (66)
Posterior circulation (%)	83 (30)	58 (31)
Not found (%)	12 (4)	5 (3)
Hijdra scores[a]		
Sum score cisterns > median of 26 (%)	126 (46)	87 (47)
Sum score ventricles > median of 3 (%)	142 (52)	84 (45)
Total sum score > median of 29 (%)	137 (50)	89 (48)
ICH present[b]	95 (35)	46 (25)
Length of ICU stay in days, median (IQR)	7 (4 – 12)	7 (4 – 16)

SOD selective oropharyngeal decontamination, *SDD* selective digestive tract decontamination, *AMC* Academic Medical Center Amsterdam, *UMCU* University Medical Center Utrecht, *UMCG* University Medical Center Groningen, *WFNS* World Federation of Neurosurgical Societies, *ICH* intracerebral haematoma, *IQR* interquartile range, *ICU* intensive care unit

[a] 10 missing

[b] 7 missing

The results for DCI and functional outcome are shown in Table 2. The primary outcome of DCI occurred in 122 (26%) patients. Survival at 28 days was missing for 28 patients (6%) and functional outcome at 3 months was missing for 76 patients (17%). For 16 of these 76 patients, functional outcome at 6 months was known and was extrapolated to the 3 months, outcome. One hundred fourteen patients (26%) had died at 28 days and 237 patients (59%) had a poor functional outcome at 3 months. There was no difference in occurrence of DCI, 28-day case-fatality or poor outcome at 3 months for the combined preventive antibiotics group (SOD and SDD) versus no preventive antibiotics (Table 2). The aHR for DCI was 0.8 (95% CI 0.4–1.6) for SOD and 1.1 (95% CI 0.6–2.0) for SDD. The aRR for 28-day case-fatality was 0.9 (95% CI 0.5–1.6) for SOD and 1.3 (95% CI 0.7–2.2) for SDD. The aRR for poor outcome at 3 months was 1.1 (95% CI 0.8–1.6) for SOD and 1.4 (95% CI 1.1–1.9) for SDD. When all 61 patients without follow-up imaging were scored as having DCI instead of not having DCI, the aHR for DCI in patients who received preventive antibiotics was essentially the same (0.9 [95% CI 0.6–1.4]). When all patients lost to follow-up were considered alive, the aRR for 28 days case-fatality in patients who received preventive antibiotics was essentially unchanged (1.2 [95% CI 0.7–1.9]).

Table 2. Outcome measures per treatment group.

	Preventive antibiotics (SOD/SDD) n = 274	**No preventive antibiotics n = 185**
DCI		
Number (%)	72 (26)	50 (27)
Unadjusted HR (95% CI)	1.0 (0.7 – 1.4)	Ref
Adjusted HR (95% CI)[a]	1.0 (0.6 – 1.8)	Ref
	Preventive antibiotics (SOD/SDD) n = 255	**No preventive antibiotics n = 176**
28-day case-fatality		
Number (%)	80 (31)	34 (19)
Unadjusted RR (95% CI)	1.6 (1.1 – 2.3)	Ref
Adjusted RR (95% CI)*	1.1 (0.7 – 1.9)	Ref

Table 2. *continued*

	Preventive antibiotics (SOD/SDD) n = 224	No preventive antibiotics n = 175
Functional outcome; mRS (%)		
0	9 (4)	16 (9)
1	22 (10)	18 (10)
2	23 (10)	32 (18)
3	20 (9)	22 (13)
4	30 (13)	28 (16)
5	26 (12)	16 (9)
6	94 (42)	43 (25)
Poor functional outcome		
Number (%)	150 (67)	87 (50)
Unadjusted RR (95% CI)	1.3 (1.1 – 1.6)	Ref
Adjusted RR (95% CI)**	1.2 (1.0 – 1.4)	Ref

SOD selective oropharyngeal decontamination, *SDD* selective digestive tract decontamination, *DCI* delayed cerebral ischaemia, *HR* hazard ratio, *RR*: risk ratio, *CI* confidence interval, *ICU* intensive care unit, *mRS* modified Rankin Scale

[a] Adjustments were made for WFNS, recurrent bleeding, treatment centre and treatment modality

DISCUSSION

In this retrospective study, no association was found between the use of preventive antibiotics and the occurrence of DCI or poor clinical outcome in aSAH patients who were admitted to the ICU within 72 h after SAH.

Several inflammatory parameters and infection, especially pneumonia, have been shown to be associated with DCI and unfavourable outcome after aSAH, which provides a window of opportunity for preventing DCI or unfavourable outcome by means of prevention of infection.[6,7,17] No previous studies have investigated the role of preventive antibiotics after aSAH, however, our results concur with recent studies on preventive antibiotic treatment in adults with ischaemic stroke and intracerebral haemorrhage showing that preventive antibiotics are unlikely to reduce mortality or poor outcome in these patients.[18,19]

Although both SDD and SOD have been proven beneficial in reducing 28-day case-fatality in the ICU population as a whole, this effect was probably not attributed to the aSAH patients, based on the results from the current study. Several explanations for the negative

result of our study should be addressed. First of all, neurogenic or central fever, as defined by fever in neurological patients without associated infection, is common in patients with aSAH in the ICU and is associated with DCI after aSAH.[20,21] Both neurogenic fever and the presence of a systemic inflammatory response syndrome (SIRS) without associated infection may have attributed to DCI or poor outcome. Further, the development of DCI is associated with other factors besides inflammation, such as larger and smaller vessel vasospasm, cortical spreading depression and microvascular thrombosis for which starting preventive antibiotics is not the all-embracing approach for decreasing the risk of DCI.[2]

Several sources of bias may explain our results. First, the decision to start SOD or SDD was based on the existing local protocol or ongoing study, and on the judgement of the treating physician who did not start SOD or SDD when the expected ICU stay was less than 72 h. This inevitably has led to confounding by indication, which might have influenced outcome. Second, we had no information on possible use of antibiotics before admission to the ICU, but considering the fact that 90% of patients were admitted to the ICU within 24 h after the ictus this probably has not affected our results. We also had no exact information on the additional use of antibiotics besides SOD or SDD treatment during ICU admission and we did not prospectively assess the occurrence of infections. However, the lacking of this information seems less relevant, as differences in inflammatory parameters or presence of infections between the groups would not alter the absence of an association between preventive antibiotics and DCI or poor outcome.

The large, multicentre consecutive series of patients and the complete data on DCI, accurately assessed based on previously defined definitions[16], are strong points of our study.

CONCLUSIONS

In conclusion, our results do not support a role of preventive antibiotics in reducing the occurrence of DCI and subsequent poor outcome in patients with aSAH admitted to the ICU. Although a positive effect of antibiotics on DCI and poor outcome cannot be excluded definitively by our results, we consider the chance of a positive effect with a larger sample size to be small, also in the light of the recent negative trials in other subsets of stroke.

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PART III

INDUCED HYPERTENSION FOR TREATMENT OF DCI

5

HIMALAIA (Hypertension Induction in the Management of AneurysmaL subArachnoid haemorrhage with secondary IschaemiA)

A randomized single-blind controlled trial of induced hypertension vs. no induced hypertension in the treatment of delayed cerebral ischemia after subarachnoid hemorrhage.

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ABSTRACT

Rationale

Delayed cerebral ischemia (DCI) is a major complication after aneurysmal subarachnoid hemorrhage (SAH). One option to treat delayed cerebral ischemia is to use induced hypertension, but its efficacy on the eventual outcome has not been proven in a randomized clinical trial. This article describes the design of the HIMALAIA trial (Hypertension Induction in the Management of AneurysmaL subArachnoid haemorrhage with secondary IschaemiA), designed to assess the effectiveness of induced hypertension on neurological outcome in patients with DCI after SAH.

Aims

To investigate whether induced hypertension improves the functional outcome in patients with delayed cerebral ischemia after SAH.

Design

The HIMALAIA trial is a multicenter, singe-blinded, randomized controlled trial in patients with DCI after a recent SAH. Eligible patients will be randomized to either induced hypertension (n = 120) or to no induced hypertension (n = 120). In selected centers, the efficacy of induced hypertension in augmenting cerebral blood flow will be measured by means of cerebral perfusion computerized tomography scanning. Follow-up assessments will be performed at 3 and 12 months after randomization by trial nurses who are blinded to the treatment allocation and management. We will include patients during five years.

Study outcomes

The primary outcome is the proportion of subarachnoid hemorrhage patients with delayed cerebral ischemia with poor outcome three-months after randomization, defined as a modified Rankin scale of more than 3. Secondary outcome measures are related to treatment failure, functional outcome, adverse events, and cerebral hemodynamics. The HIMALAIA trial is registered at clinicaltrials.gov under identifier NCT01613235.

INTRODUCTION

Delayed cerebral ischemia (DCI) is a major complication after aneurysmal subarachnoid hemorrhage (SAH), associated with a 1·5–3-fold increase in case fatality.[1-3] DCI is a clinical diagnosis occurring up to 14 days after the initial bleeding, characterized by a decrease in the level of consciousness or a new focal deficit, or both. Symptoms of DCI are seen when the cerebral blood flow (CBF) does not meet the demand of the brain tissue. Whether cerebral infarction eventually develops as a result of DCI depends on a variety of factors.[4] Despite preventative measures such as oral nimodipine and maintaining normovolemia, the incidence of DCI is estimated at 25–30%.[2,5]

For three decades, induced hypertension, used alone or in combination with hypervolemia and hemodilution, the so-called Triple-H therapy, has been used in an effort to increase CBF in patients with DCI after SAH.[6,7] The rationale for Triple-H therapy is that CBF becomes dependent on blood pressure and viscosity in those areas of the brain with vasospasm and impaired autoregulation.[8]

In a study on the effect of different components of Triple-H, the beneficial effects of induced hypertension on brain tissue oxygenation appeared to be reversed when hypervolemia was added.[9] A Cochrane review found no benefit of hypervolemia when compared with normovolemia[5], whereas another study found hypervolemia to carry more risks than benefits[10]. A previous study showed that hemodilution increased CBF but actually decreased cerebral oxygen delivery.[11] A review of the literature involving the effect of Triple-H therapy and its components on CBF showed that there is insufficient evidence that CBF improves due to the interventions. From all components, induced hypertension seems most promising in increasing CBF.[12]

The use of Triple-H or induced hypertension has been associated with an increased risk of cardiovascular and cerebral complications.[13-15] These potentially serious side-effects might negate a positive effect on the eventual outcome. This uncertainty makes that the application of induced hypertension varies widely between centers.[16]

Given all these uncertainties, we aim to perform a randomized controlled trial to assess the effectiveness of induced hypertension on neurological outcome and cerebral perfusion in patients with DCI after SAH. We will apply induced hypertension only and maintain normovolemia without aiming for hypervolemia or hemodilution.

OBJECTIVES

The primary objective is to investigate whether induced hypertension improves the functional outcome at three-months in patients with DCI after aneurysmal SAH. Secondary objectives are to investigate the effects of induced hypertension on case fatality, activities of daily living (ADL), quality of life, anxiety and depression, cognitive functioning, treatment failure, and complications related to study procedures. In substudies, we will investigate whether induced hypertension results in improved cerebral hemodynamics as measured by perfusion computerized tomography (CT) and reduced costs.

METHODS

Trial design

The HIMALAIA trial (Hypertension Induction in the Management of AneurysmaL subArachnoid haemorrhage with secondary IschaemiA), is a multicenter single-blinded randomized controlled trial on the effects of induced hypertension on outcome in patients with DCI after SAH. Eligible patients will be randomized to induced hypertension or no induced hypertension, but hypotension (defined as a mean arterial pressure below 80 mmHg) will be avoided, if necessary with vasopressors. Assessments will be performed by trial nurses who are masked for the treatment allocation and management. In a sub-study performed in selected centers, the efficacy of induced hypertension in augmenting CBF will be measured by means of cerebral perfusion CT scanning.

Patient population

Eligible patients for trial participation include all patients above 18 years with an aneurysmal SAH. Exclusion criteria for eligibility are further shown in Table 1. All eligible patients will be asked for their informed consent as soon as possible after admission. In case of a depressed level of consciousness, the patient's legal representative will be asked. Actual participation in the study will only start in subjects from whom informed consent is obtained at the moment DCI occurs, provided that all inclusion and exclusion criteria, also shown in Table 1, are fulfilled.

Randomization

When an eligible patient develops signs of DCI and fulfills criteria for participation, one of the investigators will randomize the patient by means of a computer randomization program that is stratified per center with a random block size of maximum eight.

Intervention

After randomization, patients are allocated to induced hypertension or not. Hypertension will be induced with fluids (if hypovolemia is suspected) as well as vasopressors. Positive inotropic medication can be added in case of a low cardiac output as appropriate. If the low cardiac output cannot be sufficiently reversed by this measure, the induction of hypertension should not be continued. The maximum doses of vasopressors may differ between centers. The following vasopressors can be considered: norepinephrine, dopamine, phenylephrine, and terlipressine. The dosage of vasopressors will be increased according to the protocol of the local center until the neurological deficits improve, or until any possible complication occurs that necessitates tapering of the administration of the vasopressor according to the treating physician. In addition, the maximum aimed mean arterial blood pressure (MAP) in these patients will be 130 mmHg or the maximum aimed systolic blood pressure will be 230 mmHg. The administration of vasopressors will be tapered in patients who do not show any improvement of their neurological deficits within 24 h of which at least six hours at a maximum dose as determined by the local investigator. Induced hypertension will be continued for at least 48 h when patients show some improvement within the first 24 h. After 48 h, the dose of the vasopressor will be tapered daily and resumed for at least 24 h in case of clinical deterioration.

Patients who are randomized to no hypertension will not have their blood pressure raised. Transfer to the Intensive Care Unit (ICU) will be left to the consideration of the treating physician.Vital functions will be secured, but no efforts will be made to increase blood pressure to supranormal values. Hypotension, defined as a MAP below 80 mmHg will be prevented, if necessary by means of (low dose) vasopressors.

The local SAH protocol of the participating study center will be used for other parts of medical care, and includes in all cases treatment with oral nimodipine and aiming for normovolemia.

The current recommended dose of oral nimodipine is six times 60 mg orally. In case of a significant decrease in blood pressure (defined as a decrease of at least 15 mmHg of the MAP) after the administration of nimodipine, the administration of nimodipine can be spread to 12 times 30 mg or 24 times 15 mg.

In all participants in this trial, the following procedures will be followed. A neurological examination on the level of consciousness and focal deficits will be performed and recorded at least daily during the study period and during neurological deterioration and recovery, using the Glasgow Coma Scale score and the National Institutes of Health Stroke Scale. Heart rhythm will be monitored to detect cardiac arrhythmias. A 12 skin electrodes electrocardiogram (ECG) and cardiac enzymes (CK-MB and troponin T) will be evaluated

daily during induced hypertension and for three-days in the control group to monitor possible cardiac ischemia and arrhythmias. In addition, in patients with a central venous catheter (CVC), central venous oxygen saturation will be measured, in order to estimate systemic perfusion. This will be done directly after inclusion in the trial and daily during induced hypertension and for three-days in the control group.
There is no obligation to insert a CVC solely for the purpose of this study, especially as complications of CVC insertion is a secondary outcome measure of this study.

Three months after the randomization, alive patients or their legal representatives will receive a standard questionnaire and will be asked to return the completed questionnaire. When patients are unable to complete this questionnaire, a proxy telephone interview will be held by the research nurse, who is blinded for treatment allocation and management.

The questionnaire will include the modified Rankin scale to assess the primary endpoint, as well as items on ADL (assessed with the Barthel index)[17], quality of life (estimated with the Stroke Specific Quality of Life Scale)[18-20], anxiety and depression (assessed with Hospital Anxiety and Depression Scale)[21], and cognitive functioning and perceived social functioning (evaluated by the Cognitive Failures Questionnaire)[22]. Twelve months after the randomization, patients will receive a second questionnaire on functional outcome, medical costs, and productivity losses.

Substudy on cerebral perfusion

In selected centers, we will perform a substudy to assess the influence of hypertension on cerebral hemodynamics. In these participants, two perfusion CT scans of the brain will be made: one after neurological deterioration and one 24–36 h after randomization. Cerebral blood volume, time-to-peak, and mean transit time will be used to calculate CBF in 12 predefined regions of interest. The radiologists performing the CT scan observations will be blinded for treatment allocation.

Table 1. Criteria for eligibility and randomization.

Criteria for eligibility
Inclusion criteria
Age above 18 years
SAH with an aneurysmatic bleeding pattern
Exclusion criteria
Co-existing severe head injury
Perimesencephalic hemorrhage
A history of a ventricular cardiac rhythm disorder or heart failure necessitating medical treatment
Likely transfer to another hospital, not participating in the trial, soon after treatment for the aneurysm
Moribund
Pregnancy
No informed consent
Additional exclusion criteria for the substudy on cerebral perfusion:
Known allergy for CT-contrast agents
Renal failure, defined as a serum creatinine > 150 µmol/l
Diabetes mellitus
Criteria for randomization
Inclusion criteria
DCI based on a decrease of at least one point on the Glasgow Coma Scale sumscore, and/ or the development of new focal neurological deficits according to the NIHSS, diagnosed by a neurologist, neurosurgeon or intensivist, unless the deterioration does not reflect DCI as evaluated by the treating physician.
Exclusion criteria
Another cause for neurological deterioration e.g.:
(Increasing) hydrocephalus.
Recurrent bleeding
Clinical signs of epilepsy
Severe infectious disease with associated decrease in level of consciousness.
Hypoglycemia, defined as serum glucose < 3.0 mmol/l.
Hyponatremia, defined as serum sodium < 125 mmol/l.
Metabolic encephalopathy due to renal or hepatic failure
An untreated symptomatic aneurysm
A spontaneous mean arterial pressure above 120 mmHg at the moment of randomization
Any contraindication for induced hypertension
For the substudy on cerebral perfusion:
No CT perfusion scan at time of neurological deterioration.
More than three contrast CT scans since admission.

CT computerized tomography, *NIHSS* National Institutes of Health Stroke Scale, *SAH* Subarachnoid Hemorrhage, *DCI* Delayed Cerebral Ischemia

Outcomes

The primary outcome is the proportion of poor outcome three months after randomization, defined as a modified Rankin scale of 4, 5, or death. Secondary outcome measures are listed in Table 2. In a subgroup, we will study measures of CBF (Table 3).

Table 2. Outcome measures.

Primary outcome measure
The proportion of poor outcome three months after SAH, defined as a modified Rankin scale of 4, 5, or death
Secondary outcome measures
Treatment failure:
Proportion of patients in the induced hypertension group in which induced hypertension did not give clinical improvement of symptoms of DCI within 24 hours
Functional condition:
Case fatality 30 days after SAH
Activities of daily living (ADL) three months after the SAH (Barthel Index)(17)
Quality of life three months after the SAH (Stroke Specific Quality of Life Scale, SSQoL-12-NL)(18-20)
Anxiety and depression three months after the SAH (Hospital Anxiety and Depression Scale, HADS)(21)
Cognitive functioning three months after the SAH (Cognitive Failures Questionnaire, CFQ)(22)
Functional outcome twelve months after the SAH (modified Rankin Scale).
Adverse effects:
Complications related to insertion of a central venous catheter or intra-arterial catheter (e.g. local hemorrhage and pneumothorax).
Intracranial complications related to induced hypertension (such as exacerbation of cerebral edema, hemorrhagic infarction and bleeding of an asymptomatic aneurysm).
Systemic complications related to induced hypertension (including cardiac rhythm disorders (defined as a ventricular or atrial rhythm disorder that causes medical intervention), low cardiac output state and cardiac ischemia (defined as the combination of elevated cardiac enzymes and specific EKG changes).
Costs:
Direct medical costs of used health care resources and indirect, non-medical costs of lost productivity, will be compared between the two arms of the trial, twelve months after the SAH.

SAH Subarachnoid Hemorrhage, *DCI* Delayed Cerebral Ischemia

Table 3. Substudy on cerebral perfusion – outcome measures.

The difference in CBF between the intervention and the control groups 24-36 hours after the start of the study.
The difference in CBF between the CT perfusion scan (at baseline, the moment of deterioration) and the second CT perfusion scan within the same patients.

CBF Cerebral Blood Flow, *CT* computerized tomography

Data safety monitoring board

The data safety monitoring board (DSMB) is an independent board especially appointed for this study. The DSMB consists of the biostatistician Prof. Kit C. B. Roes, (chairman, University Medical Centre Utrecht), Jacinta J. Maas (neurologist-intensivist Leiden University Medical Centre), and Astrid W. E. Hoedemaekers (internist-intensivist Radboud Medical Centre Nijmegen).

The DSMB will meet at least once every six months. A planned formal interim analysis will take place after 120 patients completed the trial. The data are provided by the trial coordinator and unblinded by a trial nurse who periodically provides the unblinded data to the DSMB. The initial frequency of reports to the DSMB will be at least every three months or after each five randomized patients (whichever is first). These reports may initiate an earlier meeting of the DSMB.

The Board may for various reasons decide to perform additional analyses. Throughout the study period, the DSMB will provide recommendations on patient recruitment, overall conduction of the trial, safety, treatment harm, and continuation of the trial.

Serious adverse events (SAEs) are reported within seven days after notification to the Central Committee on Research involving Human Subjects and the central medical ethics board. A SAE is defined according to the definition made by the Central Committee on Research Involving Human Subjects within the timeframe of hospital admission, with the remark that an infectious disease such as a pneumonia that prolongs inpatients' hospitalization will not be considered as a SAE because these infections are frequent in this patient population and are not related to the presence or absence of induced hypertension.[23]

Quality assurance and data management

Data monitoring will be performed according to a predefined monitor plan. Monitor visits will at least take place after the first, 10th, 40th, and the last included subject per center. Depending on recruitment and previous monitoring comments, monitoring visit

frequency can be adjusted. All data will be entered in an electronic Case Record Form and managed by the Clinical Research Unit of the Academic Medical Centre Amsterdam in the Netherlands.

Sample size

As 42% of SAH patients with DCI have a modified Rankin scale score of 3 or more at three-month follow-up[24], we will be able to detect a relative risk of 0·60 associated with induced hypertension, with a = 0·05 and 80% power, for which 240 patients in a 1:1 randomization are needed. To adapt to a lower randomization rate, we plan to include the needed 240 patients in five-years.

Statistical analysis

The primary analysis will be performed by 'intention to treat'. The primary analyses at study completion as well as the planned interim analyses will be based on the ratio between the treatment arms in the proportion of poor outcome after three-months and its corresponding 95% confidence interval (CI). Accounting for planned interim analyses, the confirmatory analysis at study completion will be performed at an a of 4·9%, which corresponds closely to the overall 5% level. In addition to this primary analysis, we will analyze the effect of treatment in patients who completed at least 24 h of induced hypertension without crossover to no induced hypertension vs. patients with no induced hypertension without crossover to induced hypertension (on-treatment analysis).

The secondary outcomes will be analyzed as follows: for continuous outcomes, the mean difference with 95% CI will be calculated; for categorical outcomes, risk ratios and 95% CIs will be calculated; and for ordinal outcomes, the Mann–Whitney U-test will be used. Adjustments will be made with linear regression (for continuous outcomes) and Poisson regression (for categorical outcomes) for the factors age and clinical grade at the diagnosis of DCI according to the World Federation of Neurosurgical Societies grading scale[25]. Planned subgroup analyses will be based on time from the diagnosis of DCI to start of treatment (dichotomized at the median).

Direct medical costs of used health care resources will be compared between the two arms of the trial. Costs of used health care resources will be calculated by the product of volumes of resource utilization and unit costs. Hospital days will be broken down in ICU days and ward days (and medium care unit days as appropriate). Medical costs will also include expenses of a stay in a nursing home or rehabilitation center and costs related to visits to an outpatient clinic or general practitioner as well as costs of district nursing. Effectiveness is expressed in terms of a reduced risk of poor outcome 12 months after the SAH. Incremental costeffectiveness of induced hypertension as compared with no

induced hypertension will be estimated in terms of the additional costs per prevented case of poor outcome. Uncertainty will be evaluated by means of bootstrapping. The time horizon for all analyses will be 12 months after inclusion in the proposed study.

FUNDING

HIMALAIA is a nonprofit study and was funded by de Dutch Heart Foundation (grant 2009B046) and the Netherlands Brain Foundation (grant 2009 (1-72)). The study is registered at clinicaltrails.gov with identifier NCT01613235.

SUMMARY

The HIMALAIA study is designed to assess the effectiveness of induced hypertension on neurological outcome in patients with DCI after aneurysmal SAH. Because DCI is frequently seen after SAH and increases case fatality 1·5–3-fold, it is vital to find an effective and safe treatment for this major complication. Induced hypertension has been used to treat DCI, but scientific evidence of efficacy is poor, and the treatment has been associated with an increased risk of cardiovascular and cerebral complications. Furthermore, the application of induced hypertension varies widely between centers. With this randomized clinical trial, we hope to provide the still lacking data on the efficacy and safety of induced hypertension for the treatment of DCI.

STUDY ORGANIZATION

Principal investigator: Arjen J.C. Slooter. Study coordinator: Celine S. Gathier. Executive committee: Arjen J.C. Slooter, neurologist-intensivist (chairman, UMC Utrecht), Celine S. Gathier, resident in neurology (study coordinator, UMC Utrecht), Gabriel J.E. Rinkel, neu rologist (UMC Utrecht), Walter M. van den Bergh, neurologistintensivist (AMC Amsterdam and UMC Groningen), and Paut Greebe (research nurse, UMC Utrecht). Steering committee: Arjen J.C. Slooter (chairman), Celine S. Gathier, Gabriel J.E. Rinkel, Walter M. van den Bergh and Ale Algra (clinical epidemiologist, UMC Utrecht). Data Monitoring Safety Board: Kit C.B. Roes (chairman, biostatistician, University Medical Centre Utrecht), Jacinta J. Maas (neurologist-intensivist Leiden University Medical Centre), and Astrid W.E. Hoedemaekers (internist-intensivist Radboud Medical Centre Nijmegen). Clinical Research Unit: Selma Mehmedovic (Clinical Research Assistant), Rudy A. Scholte (Data management). Clinical epidemiologist: Ale Algra. Local investigators: University Medical Centre Utrecht: Arjen J.C.

Slooter (principle investigator), Celine S. Gathier (study coordinator), Gabriel J.E. Rinkel, Bon H. Verweij, Jozef Kesecioglu, Luca Regli, Jan-Willem Dankbaar, Irene C. van der Schaaf, Ale Algra (investigators). Academic Medical Centre Amsterdam: Walter M. van den Bergh (local principle investigator), W. Peter Vandertop, Janneke Horn, Bert A. Coert, Marcella C.A. Muller (investigators). Erasmus Medical Centre Rotterdam: Mathieu van der Jagt (local principle investigator), Aad van der Lugt, Fop van Kooten, Diederik Dippel, Clemens M.F. Dirven (investigators). St. Elisabeth Hospital Tilburg: Annemarie W. Oldenbeuving (local principle investigator), Gerwin Roks, Gus N. Beute, Bram van der Pol (investigators). New members may be added if more centers join the study.

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Effects of induced hypertension on cerebral perfusion in delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: a randomized clinical trial.

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ABSTRACT

Background and purpose

The presumed effectiveness of induced hypertension for treating delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage is based on uncontrolled case-series only. We assessed the effect of induced hypertension on cerebral blood flow (CBF) in aneurysmal subarachnoid hemorrhage patients with delayed cerebral ischemia in a randomized clinical trial.

Methods

Aneurysmal subarachnoid hemorrhage patients were randomized to induced or no induced hypertension (control group) at delayed cerebral ischemia onset. CBF was assessed, blinded for treatment allocation, with computed tomographic perfusion in standardized predefined regions at delayed cerebral ischemia onset and after 24 to 36 hours of study treatment. Mean arterial blood pressure was compared between groups (linear mixed model). The primary outcome measure was the difference in change in overall CBF (Mann–Whitney U test).

Results

Mean arterial blood pressure was, on average, 12 mmHg (95% confidence interval, 8.6–14.5) higher in the hypertension group (n=12) than in the control group (n=13). Change in overall CBF (mL/100g per s) was –8.5 (range, –42 to 30) in the control group and 0.1 (range, –31–43) in the hypertension group (P=0.25).

Conclusions

Change in overall CBF did not differ to a statistically significant extent between the groups. Based on our results, 225 to 250 patients per group are needed to find a statistically significant difference in change in overall CBF between induced hypertension and no hypertension.

INTRODUCTION

Delayed cerebral ischemia (DCI) contributes to poor outcome after aneurysmal subarachnoid hemorrhage[1] and may occur when the cerebral blood flow (CBF) no longer meets the demand of the brain tissue in the setting of impaired cerebrovascular autoregulation[2]. Vasospasm is an important cause of DCI, and for many decades, the so-called triple-H therapy is used to target this potential cause of DCI. Of this triple-H therapy, induced hypertension seems most promising in increasing CBF to improve symptoms of DCI, but its presumed effectiveness is based on uncontrolled case-series only.[3] We performed a randomized controlled trial to assess the effect of induced hypertension on CBF with computed tomographic perfusion (CTP) in patients with DCI after aneurysmal subarachnoid hemorrhage.

METHODS

Study design and patients

From 2009 to 2015, we performed this study as part of a multicenter randomized controlled trial on the effectiveness of induced hypertension on clinical outcome. The study was approved by the relevant medical ethics committees (MEC 10–157). Inclusion and exclusion criteria and informed consent procedure were published previously.[4]

DCI was defined as a decrease of ≥1 point on the Glasgow Coma Scale sumscore or development of new focal neurological deficits, with exclusion of any other explanation for the deterioration, such as (increasing) hydrocephalus, recurrent bleeding, epilepsy (electroencephalography performed in case of suspicion of epilepsy), an infectious disease with associated decrease in consciousness level, hypoglycemia (< 3.0 mmol/L) or hyponatremia (< 125 mmol/L), metabolic encephalopathy caused by renal or hepatic failure or any other possible cause for deterioration as judged by the treating physician. All eligible aneurysmal subarachnoid hemorrhage patients of whom informed consent was obtained on admission were randomized at time of development of DCI in the absence of exclusion criteria for hypertension or CTP.[4] Randomization to either induced hypertension or no induced hypertension (control group) 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.

Interventions

Hypertension was induced for at least 24 to 48 hours with norepinephrine in the intensive care unit until improvement of neurological deficits, occurrence of a complication, a maximum mean arterial blood pressure (MAP) of 130 mmHg, or a maximum systolic blood pressure of 230 mmHg.[4] In the control group, MAP was not raised, but a MAP <80 mmHg was avoided with vasopressors. In this group, patients were managed either at a medium care unit or intensive care unit. In intensive-care unit-patients, MAP was continuously measured intra-arterially. Only the hourly, nurse validated measurements were obtained for statistical analyses. In patients in de the control group who remained in the medium care unit, blood pressure was measured noninvasively, at least every 4-hourly.

All patients were treated with oral nimodipine, which was started directly after hospital admission and continued during the entire admission period and received fluids aiming for normovolemia.

CTP imaging protocol and evaluation

All patients underwent CTP imaging at the time of clinical deterioration (CTP1) and after 24 to 36 hours of study treatment (CTP2), all performed on a 64- or 128-multidetector CT-scanner (Philips Healthcare, Best, the Netherlands; Siemens, Den Haag, The Netherlands), covering 40 to 80 mm, at the level of the basal ganglia and lateral ventricles.

All CTP scans were reconstructed at 5-mm slices and transferred to a workstation (IntelliSpace Portal; Philips Healthcare). CBF was estimated, blinded for treatment allocation, in 12 predefined regions of interest drawn in cortical gray matter and basal ganglia.

As primary outcome, we calculated the mean absolute CBF of all regions of interest (overall CBF) at CTP1 and CTP2 per patient. Change in overall CBF between these time points was subsequently calculated and compared between groups.

Furthermore, as secondary outcome measures, we compared between the groups the change in CBF in the patients' region of interest with the lowest absolute value of CBF at CTP1 (lowest CBF) and assessed relative measurements by comparing between the groups the change in the patients lowest interhemispheric CBF ratio (reflecting the largest perfusion asymmetry) between the timepoints (largest CBF asymmetry).

Sample size and statistical analysis

We calculated that a sample of 26 patients (13 per group) would yield a power of 80%, at a significance level of 0.05, to detect a 60% absolute difference in improvement in

overall CBF in the hypertension group versus the control group. For this explanatory study, we primarily performed on-treatment analyses, but an intention-to-treat analysis was additionally performed in case of crossover of patients. MAP over time was compared between groups (linear mixed model). The difference between groups in change in overall CBF, lowest CBF, and largest CBF asymmetry was analyzed (Mann–Whitney U test). Per group, the difference in overall and lowest CBF between CTP1 and CTP2 was assessed (Wilcoxon signed-rank test; post hoc analysis).

RESULTS

Of 36 randomized patients, 11 were excluded because one or both of the CTP scans were not performed (n=4); one of the CTP scans failed because of movement artifacts or insufficient contrast arrival (n=2) or the CTP scans were not suitable for postprocessing (n=5), leaving 25 patients with 50 CTP scans included in the study. Thirteen patients were randomized to induced hypertension and 12 to no hypertension (Table 1).

Table 1. Patient characteristics per group.

	No Induced Hypertension n=13	**Induced Hypertension n=12**	**Excluded Patients (n=11)***
Age, y, mean (SD)	59 (10.7)	54 (10.4)	68 (9.2)
Women (%)	11 (85)	7 (58)	10 (91)
Hypertension before aSAH (%)	1 (8)	2 (17)	5 (45)
Antihypertensive medication at admission (%)	0	1 (8)	4 (36)
WFNS score > 3	5 (38)	7 (58)	6 (55)
Aneurysm anterior circulation (%)	8 (62)	11 (92)	5 (45)
Hijdra sumscore > median of 27.5 (%)	6 (46)	7 (58)	8 (73)
Aneurysm treatment – clip/coil (%)	7 (54)/6 (46)	6 (50)/6 (50)	2 (18)/9 (82)
ICH present	4 (31)	3 (25)	1 (9)
Recurrent bleeding (%)	1 (8)	0	2 (18)
Age-adjusted bicaudate index > 1 (%)	4 (31)	5 (42)	2 (18)
Onset DCI, days after aSAH, mean (SD)	6.5 (4.1)	5.4(2.0)	8 (3.7)
Time between CTP1 and CTP2, h, mean (SD)	33 (9.7)	32 (7.3)	37 (11.3)**
MAP at baseline, mean (SD)	99 (10.7)	100 (15.2)	95 (12.2)

aSAH aneurysmal subarachnoid hemorrhage, *CTP1* computed tomographic perfusion during clinical deterioration, *CTP2* CTP 24-36 hours after randomization, *DCI* delayed cerebral ischemia, *ICH* intracerebral hematoma, *MAP* mean arterial blood pressure, *WFNS* World Federation of Neurosurgical Societies.

*5 patients randomized to induced hypertension and 6 patients randomized to the control group

** Available for 6 patients

One patient randomized to induced hypertension never received hypertension induction because cardiac ultrasound, performed before the intervention because of low venous oxygen saturation, revealed a previously unknown cardiomyopathy. Induced hypertension was judged contraindicated by the treating physician. This patient was primarily analyzed in the control group, but an intention-to-treat analysis and analysis with exclusion of this patient were additionally performed.

Between CTP1 and CTP2, the MAP was, on average, 12 mmHg (95% confidence interval, 8.6–14.5 mmHg) higher in the hypertension group than in the control group. All patients in the hypertension group were still receiving induced hypertension at time of CTP2. Change in overall CBF (ml/100g/min) was 0.1 (−31 to 43) in the hypertension group versus −8.5 (−42 to 30) in the control group (P=0.25). Secondary outcome measures did not differ significantly between the groups either, and all results remained similar with intention-to-treat analysis and after exclusion of the crossover case (Table 2).

Individual mean values of overall and lowest CBF are shown in the Figure. Only in the hypertension group, there was a trend toward improved CBF at CTP2 in the lowest perfused region.

Serious adverse events occurred in the hypertension and control group as follows: death 2 versus 1, pneumothorax 1 versus 0, atrial fibrillation 1 versus 0, myocardial ischemia 1 versus 0.

Table 2. Differences in change in CBF values between the groups.

	On Treatment			Intention to Treat			Crossover Case Excluded		
	No Induced Hyper-tension (n=13)	**Induced Hyper-tension (n=12)**	***P* value***	**No Induced Hyper-tension (n=12)**	**Induced Hyper-tension (n=13)**	***P* value***	**No Induced Hyper-tension (n=12)**	**Induced Hyper-tension (n=12)**	***P* value***
Change in overall CBF (median, range)	-8.5 (-42 to 30)	0.1 (-31 to 43)	0.25	-9.7 (-42 to 30)	-1.2 (-31 to 43)	0.25	-9.7 (-42 to 30)	0.1 (-31 to 43)	0.24
Change in lowest CBF (median, range)	1.0 (-23 to 41)	11.2 (-23 to 50)	0.38	1.9 (-23 to 41)	10.3 (-23 to 50)	0.50	1.9 (-23 to 41)	11.2 (-23 to 50)	0.41
Change in largest CBF asymmetry (median, range)	0.1 (-1.0 to 1.7)	0.0 (-1.5 to 2.6)	0.35	0.2 (-1.0 to 1.7)	0.0 (-1.5 to 2.6)	0.32	0.2 (-1.0 to 1.7)	0.0 (-1.5 to 2.6)	0.35

CBF cerebral blood flow(ml/100g/min).

* Mann-Whitney U test.

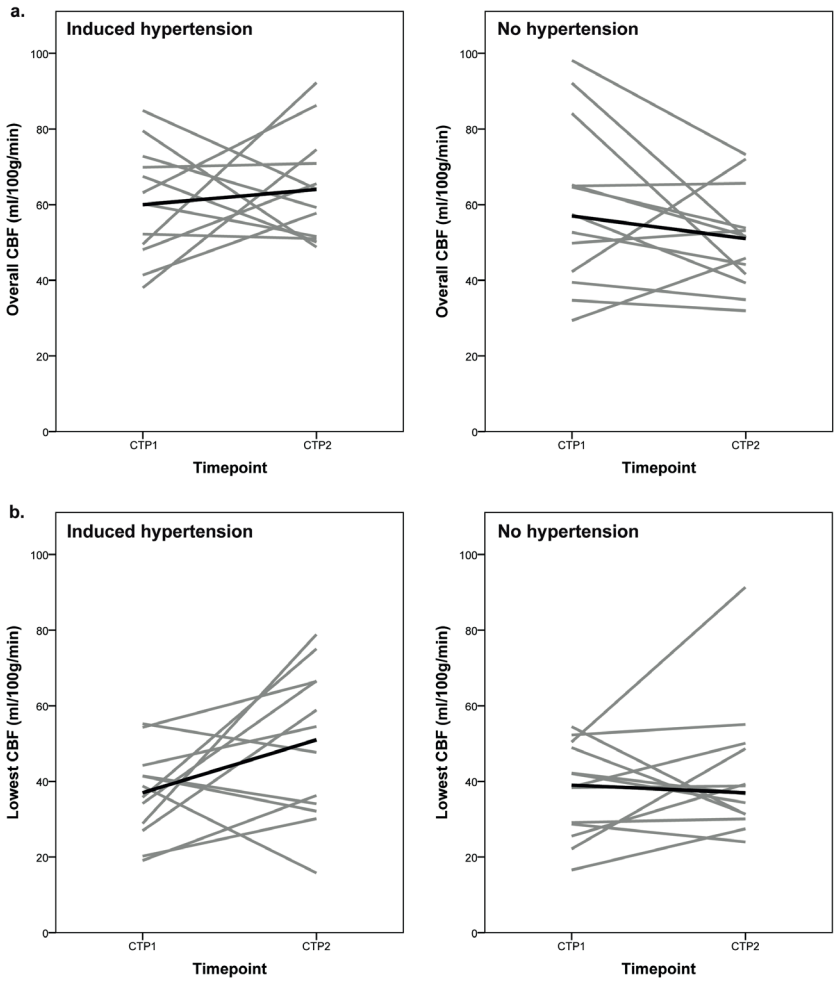

Figure. Overall (**a**) and lowest (**b**; for explanation, see text) cerebral blood flow (CBF; ml/100g/s) per patient, per time point, per group. The black line represents the median values at computed tomographic perfusion (CTP) during clinical deterioration (CTP1) and CTP 24-36 h after randomization (CTP2). **a**: Hypertension group: median overall CBF at CTP1: 60 (range, 38 – 85), median overall CBF at CTP2: 64 (range, 49 – 92), *P*=0.64. Control group: median overall CBF at CTP1: 57 (range, 29 – 98), median overall CBF at CTP2: 51 (range, 32 – 73), *P*=0.12. **b**: Hypertension group: median lowest CBF at CTP1: 37 (range, 19 – 55), median lowest CBF at CTP2: 51 (range 16 – 79), *P*=0.05. Control group: median lowest CBF at CTP1: 39 (range, 17 – 54), median lowest CBF at CTP2: 37 (range, 24 – 91), *P*=0.51.

DISCUSSION

We investigated the effects of induced hypertension alone because hypervolemia and hemodilution were earlier found not promising in increasing CBF.[3] CTP is of practical use and provides accurate estimation of CBF.[5]

Several limitations of our study are inherent to using CTP. By assessing CBF in predefined regions, we might have missed areas with more severe perfusion deficits. Selecting regions in visible areas of hypoperfusion could result in more pronounced changes in CBF but also observer bias. Second, although perfusion measurements with CTP have been validated[6], exact quantification remains difficult. For this reason, we also analyzed relative CBF measurements by comparing both hemispheres. However, when solely using this approach, bilaterally decreased perfusion can be missed.

Furthermore, 11 patients were excluded from the study because of unavailable CTP data. However, because in most cases exclusion was caused by technical problems, we believe the CTP data were missing at random and the likelihood of selection bias to be low. The greater proportion of highgrade WFNS (World Federation of Neurosurgical Societies) patients in the hypertension group may, however, have biased the results. Patients in the hypertension group were more often admitted to the intensive care unit than patients from the control group. As outcome assessment was blinded, it is unlikely that this would have affected our results.

Strengths of the study are the randomized controlled design allowing for more firm conclusions than in previous uncontrolled studies, and the achievement of a significantly higher MAP in the hypertension group.

Our findings do not support the use of induced hypertension to augment overall CBF in aneurysmal subarachnoid hemorrhage patients with DCI. However, a small effect cannot be 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. Based on our results, 225 to 250 patients per group would be needed to find a statistically significant difference in change in overall CBF between induced hypertension and no hypertension.

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Induced hypertension for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: a randomized clinical trial.

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ABSTRACT

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.

INTRODUCTION

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

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 mmHg 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 mmHg, or a systolic blood pressure of 230 mmHg. 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 mmHg 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]

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 sumscore > 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 months, 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)	

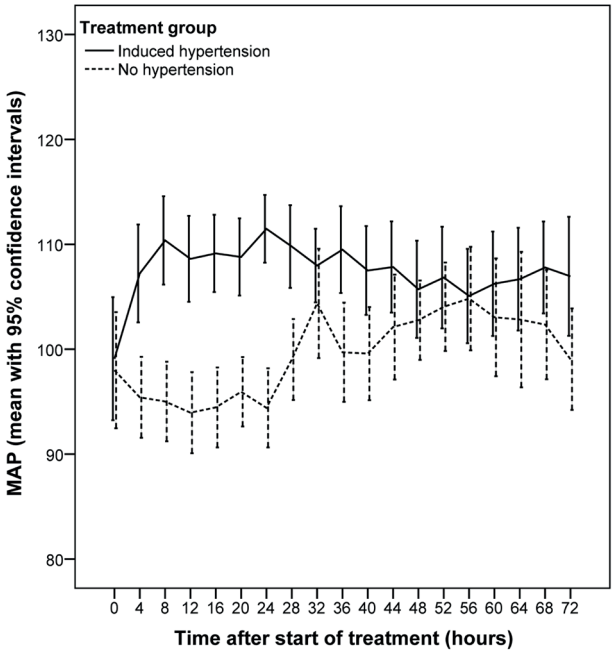
ADL activities of daily living, *aSAH* aneurysmal subarachnoid hemorrhage, *CFQ* Cognitive Failures Questionnaire, *CI* confidence interval, *CT* computed tomography, *DCI* delayed cerebral ischemia, *HADS* Hospital Anxiety and Depression Scale, *IQR* interquartile range, *MAP* mean arterial pressure, *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.

The MAP over the first 24 hours was 11.1 mmHg (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 mmHg (95% CI, 4.2–8.5 mmHg; Figure 1). 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 mmHg.

Figure 1.



MAP Mean arterial pressure over time per group.

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, 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.

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.

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 (totaling 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).

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%

Reference	Prospective	Nr. Int/No Int.	Control Group	DCI Definition	Intervention	Clinical Response	Functional Outcome	Complications
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%

Reference	Prospective	Nr. Int/No Int.	Control Group	DCI Definition	Intervention	Clinical Response	Functional Outcome	Complications
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%
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%

Reference	Prospective	Nr. Int/No Int.	Control Group	DCI Definition	Intervention	Clinical Response	Functional Outcome	Complications
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%

Reference	Prospective	Nr. Int/No Int.	Control Group	DCI Definition	Intervention	Clinical Response	Functional Outcome	Complications
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 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.

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 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.

CONCLUSIONS

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.

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8

Slow recruitment in the HIMALAIA Study: lessons for future clinical trials in patients with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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Submitted to Trials

ABSTRACT

Background

There was slower recruitment than expected in a randomized clinical trial on induced hypertension in patients with delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage (aSAH) wherein informed consent was asked on admission and randomization performed at time of DCI. We assessed the reasons for the slow recruitment, aiming to facilitate the design of future randomized trials in aSAH patients with DCI.

Methods

Efficiency of recruitment and factors influencing recruitment were evaluated, based on the patient flow in the two centers that admitted most patients during the study period. We collected numbers of patients who were screened for eligibility, provided informed consent, developed DCI and who eventually were randomized.

Results

Of the 862 aSAH patients admitted in the two centers during the course of the trial, 479 (56%) were eligible for trial participation of whom 404 (84%) where asked for informed consent. Of these, 188 (47%) provided informed consent, of whom 50 (27%) developed DCI. Of these 50 patients, 12 (24%) could not be randomized due to a logistic problem or a contraindication for induced hypertension emerging at the time of randomization, and four (8%) were missed for randomization. Eventually, 34 patients were randomized and received intervention or control treatment.

Conclusions

Enrolling patients in a randomized trial on treatment strategies for DCI is laborious, with 1 out of 25 admitted and 1 out of 14 eligible patients eventually randomized. These rates, caused by a large proportion of ineligible patients, a small proportion of patients providing informed consent and a large proportion of patients with contra-indications for treatment, can be used to make sample size calculations for future randomized trials on treatment strategies for DCI. Facilitating informed consent through improved provision of information on risks and treatment of DCI and study procedures may result in improved enrolment.

BACKGROUND

Delayed cerebral ischemia (DCI) occurs in around 30% of aneurysmal subarachnoid hemorrhage (aSAH) patients between day 3 and 14 after the initial hemorrhage and is an important contributor to poor outcome.[1] Although several treatment strategies for DCI have been investigated[2], only one randomized trial has been published on a strategy to treat DCI[3].

One of the reasons for the lack of trials in this condition may be that obtaining informed consent from patients at the time they develop DCI can be challenging. Patients with DCI often cannot provide informed consent themselves because of an impaired level of consciousness, and thus consent should be obtained from proxies. Obtaining timely informed consent from proxies is also challenging as the investigated treatment has to be installed as soon as possible after the onset of symptoms. For our randomized clinical trial in patients with DCI, in which we investigated the effectiveness of induced hypertension on cerebral perfusion and clinical outcome (the HIMALAIA study[3,4]), we therefore developed another approach of asking informed consent and performing randomization. All eligible patients, or their legal representatives in case of a depressed level of consciousness, were asked for informed consent as soon as possible after admission. Randomization was only performed at time of development of DCI.

Despite this approach, recruitment was too slow. We aimed to explore the reasons for the slower than expected recruitment to facilitate the design of future randomized trials in aSAH patients with DCI.

METHODS

From February 2009 until January 2015, the HIMALAIA Study was performed in four centers in the Netherlands.[3,4] The in- and exclusion criteria for trial participation are shown in Table 1.

From the four centers, two (the Amsterdam University Medical Center, location Academic Medical Center (AMC, 5 included patients) and the Elisabeth-TweeSteden Hospital, Tilburg (ETZ, 2 included patients)) were not included in the present study, because both included patients for only 2 years and are therefore not representative for the course of the trial. For the current study, we assessed the course of the trial in the two centers that screened most patients: the University Medical Center Utrecht, Utrecht (UMCU, 26 included patients) and the Erasmus MC University Medical Center, Rotterdam (EMC, 8 included patients).

In both centers, all aSAH patients were screened for eligibility as soon as possible after hospital admission by the study team. Informed consent was asked from eligible patients or their legal representatives in case the patient had an impaired level of consciousness by the principle investigator, study coordinator or resident in neurology who was specifically trained for the informed consent procedure of the trial. Informed consent was asked as soon as possible after hospital admission during office hours. The verbal information consisted of information about the rationale of the trial, the randomization procedure, detailed information about the possible effect and side-effects of induced hypertension, and the additional burden associated with trial participation (transfer to the Intensive Care Unit (ICU) in case of randomization to induced hypertension, an additional computerized tomography-perfusion scan (CT-perfusion) in case of participation in the CT-perfusion sub-study and a telephone interview at 3 and 12 months after hospital admission). Besides verbal information, the patient or his/her representative was also given written information about the trial. This consisted of a 4-page information document containing all information that was also provided verbally. Patients or legal representatives were always allowed at least one day to consider trial participation, and additional verbal information was provided when asked for. If consent was provided, a notification was made in the patient's medical file and all involved medical personnel was informed. Randomization was performed only in patients who developed DCI, as soon as possible after diagnosis of DCI. During the course of the trial, four investigators took shifts for the trial telephone; a phone number that could be called 24 hours per day for discussing randomization of potential candidates. The medical personnel was instructed to call the trial number as soon as a patient in whom informed consent was obtained developed signs of clinical deterioration, and to order a CT scan of the brain and blood examination according to the trial protocol. In the meantime, the trial investigator checked for the availability of an ICU bed, if the patient was not yet in the ICU, to be able to facilitate induced hypertension. As soon as other causes for the clinical deterioration had been ruled out, an ICU bed was available, and no contra-indications for induced hypertension had developed after informed consent was provided, randomization was performed by the investigator using a computer randomization program.

From the prospectively collected screening and enrollment logs and additional review of the medical files, we extracted 1) how many aSAH patients were admitted within the risk period for development of DCI, defined as admission < 14 days after ictus, 2) how many were screened for eligibility, how many eligible patients were contacted, 3) how many provided informed consent, 4) how many of these patients developed DCI, and 5) how many could eventually be randomized. Apart from the patients who participated in the trial, we assessed from the medical files whether DCI developed in patients who did not participate in the trial. The medical ethics committee of the UMCU and EMC

waived the need for informed consent for the current study on recruitment (protocol numbers 15-486/C and MEC-2012-170 respectively).

RESULTS

From February 2009 until January 2015, 862 aSAH patients were admitted to the UMCU (n=672) or EMC (n=190). Figure 1 shows in detail how patients were retrieved for the trial. Of the 862 aSAH patients admitted during the course of the trial, 479 (56%) were eligible for trial participation. Patient characteristics are shown in Table 2.The reasons for non-eligibility are provided in Table 3. The most frequent reasons were moribund status, the absence of a symptomatic aneurysm or the impossibility to (entirely) treat the aneurysm. Sixteen patients (1,9% of all screened patients) were incorrectly deemed ineligible. Of the 479 eligible patients, 75 (16%) were not approached for informed consent, of whom 19 developed DCI and thus could potentially have been candidates for trial participation after informed consent. Of the 404 (84%) patients who were approached for informed consent, 188 (47%) provided it, of whom 50 (27%) developed DCI (figure 1). Of these 50 patients, 34 (68%) could be randomized (26 in the UMCU and 8 in the EMC), and managed according to intervention or control treatment. In 12 (24%) patients, randomization could not be performed: in five patients, baseline blood pressure was too high, in three patients the deterioration rapidly improved spontaneously, in two patients there was initial doubt whether the deterioration was based on DCI, one patient developed DCI just after transfer to another hospital and in one patient no ICU bed was available. Four (8%) patients were not randomized despite absence of contraindications for induced hypertension.

Table 1. Criteria for eligibility and randomization.

Criteria for eligibility
Inclusion criteria
Age above 18 years
SAH with an aneurysmal bleeding pattern
Exclusion criteria
Evidence of DCI after the SAH, unless symptoms of DCI started within 3 hours.
Coexisting severe head injury
Perimesencephalic hemorrhage
A history of a ventricular cardiac rhythm disorder or heart failure necessitating medical treatment
Likely transfer to another hospital, not participating in the trial, soon after treatment for the aneurysm
Moribund
Pregnancy
No informed consent or informed consent not feasible
Additional exclusion criteria for the sub-study on cerebral perfusion
Known allergy for CT contrast agents
Renal failure, defined as a serum creatinine > 150 μmol/L
Diabetes mellitus and glomerular filtration rate < 60
Criteria for randomisation
Inclusion criteria
DCI based on a decrease of at least 1 point on the Glasgow Coma Scale sum-score, and/or the development of new focal neurological deficits according to the NIHSS, diagnosed by a neurologist, neurosurgeon, intensivist, unless the deterioration does not reflect DCI as evaluated by the treating physician
Exclusion criteria
Another cause for the neurological deterioration, e.g.:
(Increasing) hydrocephalus
Recurrent bleeding
Clinical signs of epilepsy
Severe infectious disease with associated decrease in level of consciousness
Hypoglycemia, defined as serum glucose < 3.0 mmol/L
Hyponatremia, defined as serum sodium < 125 mmol/L
Metabolic encephalopathy due to renal or hepatic failure
Ischemia related to aneurysm treatment
An untreated symptomatic aneurysm
A spontaneous mean arterial pressure above 120 mmHg at the moment of randomization
Any other contraindication for induced hypertension
No CT-perfusion scan at time of neurological deterioration
More than three contrast CT scans since admission

CT computerized tomography, *NIHSS* National Institutes of Health Stroke Scale, *SAH* subarachnoid hemorrhage, *DCI* delayed cerebral ischemia.

Table 2. Patient characteristics.

	All patients (n=862)	**Eligible (n= 479)**	**Not eligible (n=383)**
UMCU / EMC (%)	672 (78%) / 190 (22%)	373 (78%) / 106 (22%)	299 (78%) / 84 (22%)
Age, mean (SD)	59 (13)	57 (12)	61 (14)
Female (%)	603 (70%)	359 (75%)	244 (64%)
Medical history of hypertension	256 (30%)*	122 (26%)**	134 (35%)***
Admission-WFNS score > 3	373 (43%)	148 (30%)	225 (59%)
Anterior circulation aneurysm (%)	506 (59%)	328 (68%)	178 (46%)
No aneurysm with aneurysmal bleeding pattern	97 (11%)	-	97 (25%)
Aneurysm treatment			
- Clip	254 (30%)	208 (43%)	49 (13%)
- Coil	365 (42%)	271 (57%)	93 (24%)
- No aneurysm treatment (%)	243 (28%)	-	241 (63%)

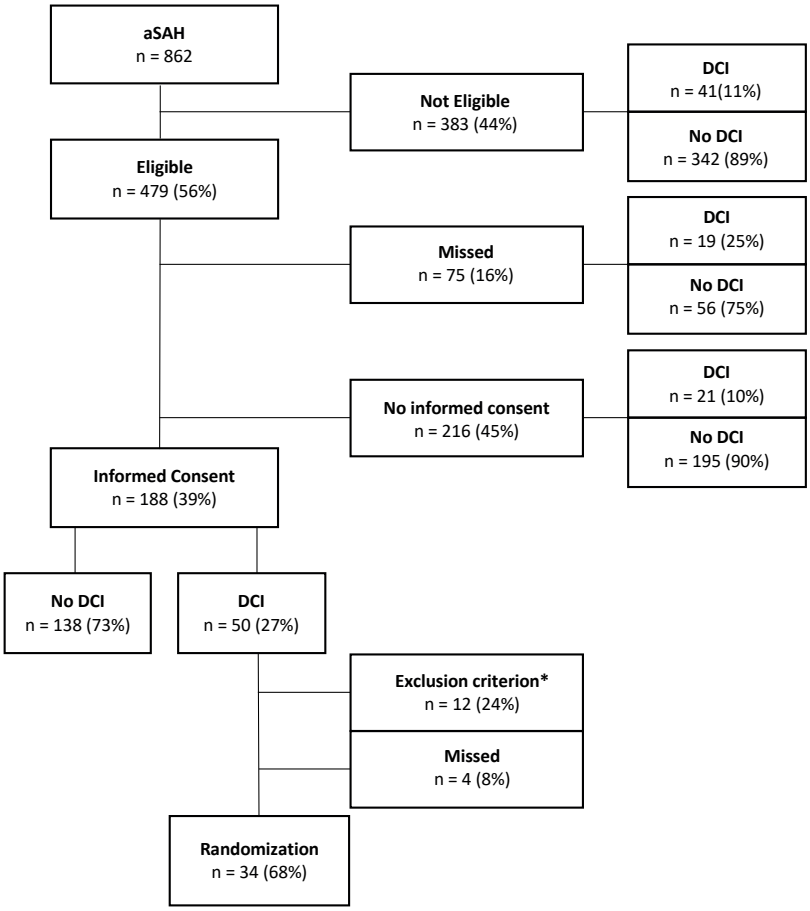
UMCU University Medical Center Utrecht, *EMC* Erasmus MC University Medical Center, *SD* standard deviation, *WFSN* World Federation of Neurosurgical Societies scale, *DCI* delayed cerebral ischemia. *missing for 10 patients. ** missing for 1 patient. *** missing for 9 patients.

Table 3. Reasons for non-eligibility for the trial.

	Number of patients n=383
Reasons for ineligibility	
Contra-indication for participation	367 (96%)
Moribund on admission	160 (44%)*
No aneurysm found	67 (18%)
Aneurysm could not (entirely) be treated	47 (13%)
Partial coiling	9
Delayed aneurysm treatment due to severe vasospasm	11
Aneurysm treatment technically not possible	27
Signs of DCI on admission	23 (6%)
Cardiac contra-indication for iHT	18 (5%)
Transfer to another hospital	17 (5%)
Contraindication for CT-contrast agent	10 (3%)
Non- cardiac contra-indication for iHT	7 (2%)
No Dutch or English	6 (2%)
Legally incompetent patient without a legal representative present	5 (1%)
DCI immediately after treatment of the aneurysm	3 (1%)
Admission after DCI risk period**	1 (0.3%)
Pregnancy	1 (0.3%)
Treatment restriction requested by family	1 (0.3%)
Initially not recognized aSAH	1 (0.3%)
Incorrectly deemed not eligible	16 (4%)
Delayed admission to the hospital without any signs of DCI yet	5 (31%)
Not asked for informed consent due to misinterpretation of the in- and exclusion criteria for eligibility while they were actually eligible	11 (69%)

DCI delayed cerebral ischemia, *iHT* induced hypertension, *aSAH* aneurysmal subarachnoid hemorrhage.
*3 patients eventually did not die during admission. **admission after the risk period for DCI had already passed, defined as admission after 14 days after the initial hemorrhage.

Figure 1. Flowchart of inclusion of patients.



aSAH aneurysmal subarachnoid hemorrhage, *DCI* delayed cerebral ischemia.
* Blood pressure already too high (n=5), spontaneous improvement (n=3), initial doubt whether the deterioration was based on DCI (n=2), DCI developed just after transferal to another hospital (n=1), no ICU bed available (n=1). For detailed description of exclusion criteria, see text in methods section.

DISCUSSION

We found several factors explaining the slower than expected recruitment. Almost half the patients admitted during the study period were not eligible for the trial, of those who were eligible more than half declined participation in the trial, and of those who developed DCI one third could not be randomized due to emerging contra-indications for induced hypertension or a logistical problem.

A substantial proportion of patients was ineligible. However, no unexpected reasons were seen for ineligibility. The small number of patients incorrectly deemed ineligible will not have had major impact on the slow inclusion rate.

Only half of eligible patients provided informed consent, which was a smaller proportion than anticipated. In other randomized trials in which either the informed consent procedure was complex[5], or subjects were critically ill and admitted to the ICU[6-8], the proportion of eligible patients providing informed consent ranged from 75 to 82%. In our trial, patients or their legal representatives were asked for informed consent in case DCI would occur. This procedure was chosen to be able to initiate induced hypertension as early as possible after onset of DCI symptoms. However, it may very well be that the complexity of our informed consent procedure was an important reason for the small proportion of patients providing informed consent. Patients or legal representatives may find it difficult to imagine whether they want (their family member) to be treated with induced hypertension or not, in a possible future setting of clinical deterioration. We have no empirical data to support or refute this hypothesis. We also did not systematically assess whether the proportion of obtained informed consent differed when asked by a member of the study team (the principle investigator or study coordinator) as opposed to a resident in neurology. However, we aimed to minimize this difference by individually training the residents beforehand. Due to the fact that we did not systematically assess the reasons for declining informed consent, our study cannot provide solid recommendations. We suggest to systematically assess factors that might influence recruitment as a secondary outcome in a future clinical trial in DCI patients.

A substantial proportion of the patients who provided informed consent and developed DCI could eventually not be randomized due to the presence of either a contraindication for induced hypertension, a logistical boundary such as unavailability of an ICU bed, or because they were not asked (missed) for randomization. Under ideal circumstances, the number of additional patients that could have been randomized is 44 (19 eligible patients who were missed for informed consent and developed DCI, 21 patients who were eligible but did not provide informed consent and developed DCI and 4 patients who were eligible, provided informed consent, developed DCI but were missed for randomization).

This would have resulted in a total of 78 patients randomized over the course of 6 years (1 out of 11 admitted and 1 out of 6 eligible patients). Also, the numbers of DCI patients that were truly missed either for informed consent (n=19) or for randomization (n=4) were small, and therefore we feel that this would not have major impact on the inclusion rate.

The overall frequency of DCI in the subset of eligible patients was 19% and in the subset of patients who provided informed consent 27% which was in line what was expected and used in the sample size calculation for the trial. Therefore, the frequency of DCI itself has probably not influenced the recruitment in our trial.

FUTURE DIRECTIONS

As we considered our complex informed consent procedure an important contributor to the small proportion of informed consent, other approaches for asking informed consent might be more successful. Various other informed consent procedures are possible, such as the 'deferred informed consent' method[9,10], the "Trials within Cohorts" method or the 'just-in-time' consent method[11-13]. However, with these methods, all or a proportion of patients are not informed beforehand about the study. Withholding this information when there is actually time to provide it as we have shown in our study is in our view not ethical and not in line current European guidelines[14]. Therefore, we would still advice the method that we have used for obtaining informed consent.

However, strategies to facilitate decision making for patients or legal representatives should be explored, such as providing leaflets or short video's that can be viewed by patients and/or relatives in their own time, containing detailed information on DCI, it's consequences and the treatment. Video-assisted informed consent improves patients' understanding of the proposed treatment or intervention both in clinical practice as in research[15,16] and may result in faster enrolment with improved enrolment of minorities[17,18].

Inclusion rates could also be improved by improving the detection of patients with DCI. Especially in patients with a poor clinical condition, development of DCI can be missed when they are monitored by clinical examinations only. Additional diagnostics, such as transcranial doppler ultrasonography, brain perfusion imaging, and invasive brain multimodality monitoring may improve the timely diagnosis of DCI in these patients.[19] However, as these methods are often expensive and laborious with requirement of specific expertise and devices, they are unpractical in clinical practice and could be a complicating factor for successful implementation of a randomized clinical trial.

To bypass the difficulties associated with designing and conducting a randomized controlled trial on treatment strategies for DCI patients, a different approach could be to evaluate the effectiveness or safety of an intervention in real-life practice by using data that are obtained during routine clinical care (observational comparative effectiveness research (CER).[20] Even though data can be collected quickly and easier than in a randomized trial, bias is inevitable which will always prevent providing solid evidence based recommendations. We would therefore advocate improvement of clinical trials in DCI patients.

CONCLUSIONS

Recruitment in the HIMALAIA trial was mainly hampered by the small proportion of patients providing informed consent and the large proportion of ineligible patients. These are important findings as they can be used for the design and for sample size calculations for future randomized trials on treatment of DCI patients, aiming to increase the possibility of successful completion of such trial. Improving the informed consent method and detection of DCI in poor grade aSAH patients are important implications for further research and thus we urge future researchers to seek multicenter collaboration in trying to find better treatment options for patients with DCI.

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PART IV

GENERAL DISCUSSION

9

General discussion and future directions

In this thesis, potentially modifiable risk factors for delayed cerebral ischaemia (DCI) after aneurysmal subarachnoid haemorrhage (aSAH) have been explored and the efficacy of induced hypertension as treatment for DCI has been investigated. The results are discussed in the following sections, followed by suggestions for future research.

PATHOPHYSIOLOGY OF DCI

To explore options for prevention and treatment of DCI, it is important to first address its pathophysiology. Simply put, DCI occurs when the cerebral blood supply no longer meets the demand of the brain tissue. However, the underlying mechanism for this insufficient cerebral blood supply is not simple at all.

Cerebral vasospasm from major intracranial arteries has long been considered the most important factor leading to DCI. In the presence of cerebral vasospasm, the cerebral arteries lose their capacity to dilate their diameter (i.e. adjust cerebrovascular resistance) to vary cerebral perfusion pressure. This impaired cerebral autoregulation (CA) increases the risk of impaired cerebral blood flow.[1-10] However, vasospasm from major intracranial arteries is not the only factor resulting in impaired CA, with impaired CA also occurring without the presence of vasospasm in these arteries and vice versa.[11] Further, not all patients with vasospasm develop DCI, and not all patients with DCI show vasospasm.[12] This led to the now widespread accepted concept that multiple factors in addition to vasospasm from major intracranial arteries contribute to the development of DCI, including impaired CA due to spasm in the microcirculation, microthrombosis, inflammation and cortical spreading depression.[13] Well-established risk factors for DCI, such as the amount of extravasated blood and initial neurological status[14] reflect the severity of early brain injury which probably results in increased risk of all the above mentioned factors that contribute to the development of DCI.

Because of the complex and incompletely understood pathophysiology of DCI, many different strategies have been investigated in order to better prevent or treat DCI. The additional strategies that were investigated in this thesis are discussed in the following sections.

RISK OF DCI

Haemorrhage volume

The association between the amount and distribution of extravasated subarachnoid blood on the initial non-contrast CT scan with vasospasm was found almost 40 years ago, leading to the development of the Fisher scale for qualifying the amount of subarachnoid blood.[15] Since then, the association between the amount of cisternal and intraventricular haemorrhage (IVH) with cerebral vasospasm[16-18] and DCI[18-27] has been well established. This has led to the development of the modified Fisher scale[28] and the Hijdra sum score[21], both incorporating the amount of cisternal and intraventricular blood. The three scales (Fisher scale, modified Fisher scale and Hijdra sum score) are all associated with DCI[29,30] and are used in prediction models for DCI. Accurate prediction of DCI is important, as this might improve outcome in patients at high risk for DCI if well-established treatment for DCI becomes available, and prevent futile intensive care monitoring in patients at low risk.[13] Unfortunately, the current prediction models have only poor to moderate discriminative power.[14,31] This might be partially caused by the moderate interobserver agreement of the Fisher and modified Fisher scale[29,32,33], limiting the potential power of amount of blood as predictor for DCI. The interobserver agreement of the Hijdra sumscore is better, but the score is more time-consuming to calculate and therefore less practical in clinical practice.[29]

Automatic quantitative volume measurement for assessing the amount of subarachnoid blood is less observer-dependent and is very accurate compared with manual assessment.[34] In our study, we found that automatically quantified total haemorrhage volume (including cisternal haemorrhage, subdural haematoma, intraparenchymal haematoma and intraventricular haematoma (IVH)) was significantly associated with the occurrence of DCI, with an increasing association per ml of haemorrhage volume (**Chapter 2**[35]). In our study, the presence of IVH was also significantly associated with DCI. However, the latter was not confirmed in a (smaller) follow-up study[36] and therefore this association is less clear.

Recently, a prediction model was developed including automatically quantified total haemorrhage volume as a candidate predictor for DCI in addition to other clinical and radiological variables.[37] Total haemorrhage volume was found to be an independent predictor of DCI. However, even though the predictive value of the automatically quantified total haemorrhage volume was better than that of the Fisher and modified Fisher scale, it was still only moderately predictive, and not better than the existing prediction models.[14,31,38-40]

Total haemorrhage volume thus can provide an indication of which patients are at risk for DCI but does not yet discriminate well enough for use in the clinical setting. To improve prediction of DCI, other clinical, biochemical and radiological factors associated with DCI besides already established factors, need to be identified. One factor which should be further investigated, is early brain injury.

Early brain injury (EBI) refers to the acute effects of the subarachnoid blood following aneurysm rupture. The initial haemorrhage results in a rise in intracranial pressure (ICP) and a decreased cerebral blood flow (CBF).[41] The following transient global ischaemia is mediated by a complex mechanism of multiple factors such as blood-brain barrier disruption, microcirculatory constriction, microthrombosis, cortical spreading depolarisation, brain oedema and cell death. Further, it leads to systemic complications through activation of the sympathetic nervous system, such as pulmonary oedema, Takotsubo cardiomyopathy, hyponatraemia and systemic inflammatory response syndrome, which might further compromise cerebral blood flow.[41,42] The severity of EBI can be clinically reflected by the neurological grade on admission and the absence or presence of loss of consciousness, which explains why these factors are associated with poor outcome after aSAH.[43,44] As these factors are also related to increased risk of DCI[14], it is plausible that EBI is also associated with DCI. In fact, several studies have investigated surrogate markers for EBI and its association with DCI. Radiographic surrogate markers such as the amount of cerebral oedema[45], the presence of early ischaemia on MRI[46,47] or CT-perfusion[48,49] and changes in tissue permeability reflecting blood-brain barrier disruption as measured with CT-perfusion[50] have been found associated with development of DCI. Several biochemical surrogate markers for EBI have also been found associated with DCI, such as platelet activation factors and inflammatory factors[51,52] and matrix metalloproteins[53]. Further research should focus on improving the prediction of DCI when incorporating such surrogate markers of EBI.

Further, the accuracy of prediction models might be improved by using computer science such as Machine Learning. Machine Learning algorithms can learn patterns from large datasets with multiple variables, taking all their interactions into account.[54] The advantage of this method is that it can be applied to heterogenous data (data from different sources such as clinical and radiological characteristics) and that the number of variables included in the algorithm is not restricted to the number of outcome events as is the case with conventional regression models.[54-56] A recent study showed that using Machine Learning algorithms incorporating both clinical and imaging data improved the prediction of DCI in aSAH patients and also identified possible new predictors of DCI.[57]
As the amount of extravasated blood is associated with the occurrence of DCI, increased clearance of the amount of blood might serve as a potential target for preventing DCI.[58] In several retrospective studies and two small randomized clinical trials, removal of blood

via external ventricular drain, lumbar drain or other clot removal techniques showed potential benefit in reducing vasospasm[59,60] or DCI[59-63], but it's effect is not unequivocally established.

As the removal of blood via lumbar drainage is dependent on and therefore hampered by cerebral spinal fluid (CSF) production rate, a recent small single-arm safety trial assessed whether filtration of the CSF would allow for more rapid and controlled blood removal.[64] The filtration technique resulted in successful and safe removal of red blood cells from the CSF, but the effect on DCI and other clinical outcome parameters were not assessed in this small study. Future research might elucidate whether clot removal therapy could result in improved prevention of DCI.

Blood pressure

Despite extensive research on preventive strategies for DCI, the only proven drug that reduces the risk of DCI is the calcium antagonist nimodipine, probably through influencing cortical spreading ischaemia, one of the contributing factors leading to DCI.[65-68] General measures are equally important, such as preventing hyponatraemia, preventing infection, treating complications such as hydrocephalus and infection, and avoiding low blood pressure and hypovolaemia.[69,70]

When focusing on avoidance of low blood pressure, which blood pressure is actually too low for aSAH patients? As pointed out before, cerebral autoregulation (CA) is responsible for maintaining adequate blood supply to the brain.[71-73] In healthy subjects with normal blood pressure, CA can maintain constant cerebral blood flow (CBF) between a mean arterial pressure (MAP) of approximately 60 to 170 mmHg.[74] In aSAH patients, the lower and upper limits of the autoregulatory range may have changed in certain areas, with impaired CA occurring below a MAP of 70 mmHg as compared to below 60 mmHg[74]; a phenomenon that occurs independent of the presence of vasospasm[75,76]. Why this happens is not entirely clear, but might be the result of decreased capacity of the constricted arteries to respond to dilator stimuli (shift in the lower limit) and an increased tolerance of the vessels to hypertension (shift in the upper limit).[74] Previously sufficient blood pressure values might therefore become insufficient resulting in impaired CBF and an increased risk of DCI.

Although the association between impaired CA and DCI[2-10] and outcome[77-79] is well-established, the association between blood pressure and DCI is not. Clinical signs of DCI were seen more often in patients with a fall in blood pressure than in patients without, but this fall in blood pressure preceded DCI in only in 5,5% of DCI patients.[80] In some studies, intraoperative hypotension was associated with DCI[81-83], and a recent small matched case-control study suggested that DCI could be prevented by keeping intraoperative sBP

above 95 mmHg, diastolic blood pressure above 50 mmHg and MAP above 62 mmHg[84]. However, intraoperative hypotension was not related to DCI in another study[85], and a recent large retrospective observational study of 1099 patients showed no association between intra-operative hypotension and poor outcome after aSAH[86]. Further, in one study, MAP three days before DCI was actually slightly higher in patients who developed DCI as opposed to patients who did not develop DCI.[87]

Our own study was performed in a population of 1167 aSAH patients admitted to the intensive care unit (ICU), of whom 110 (9%) developed DCI during ICU admission (**Chapter 3**). We assessed the time-dependent association between blood pressure and DCI. We found a statistically significant association between a MAP of 60 mmHg or lower in the 24 hours preceding DCI and the occurrence of DCI (MAP 60 mmHg: adjusted hazard ratio 1.79, 95% confidence interval 0.99 – 3.24; MAP 50 mmHg: adjusted hazard ratio 2.59, 95% confidence interval 1.12 – 5.96).

The association we found is difficult to compare to the conflicting results of the abovementioned studies, and is further complicated by the varying methods that were used both in patient selection and in definition and analysis of blood pressure. Therefore, and unfortunately, it remains unclear to what extend blood pressure is associated with DCI.

There were several limitations to our study. First of all, blood pressures in the ICU are kept within predefined limits, as was also mostly the case in our population. Therefore, we were only able to investigate the variation in blood pressure within these limits. This might make our results less generalizable to an aSAH population not admitted to the ICU. Further, we had no information on premorbid hypertension, which is important as uncontrolled chronic hypertension can cause a premorbid raise in the lower (and upper) limit of the autoregulatory range[88,89] making patients more prone to insufficient CBF in the presence of low blood pressure[90]. Also, it might have been that we 'missed' diagnoses of DCI due to the retrospective nature of the study and the fact that clinical signs of DCI can be difficult to detect in aSAH patients admitted to the ICU. Finally, a uniform definition of hypotension is currently not available as is highlighted by the extensive research on intraoperative hypotension.[91,92] As a result, it remains unclear which blood pressure values or characteristics should be investigated in DCI patients.

The association we found between a MAP of 60 mmHg or lower in the 24 hours preceding DCI and increased risk of DCI concurs with the lower limit of a MAP of 60 mmHg below which the autoregulatory mechanisms start to fail in aSAH patients.[73,74] This may suggest that the extend of impairment of CA is more important than the actual blood pressure values and that this can vary between individual patients and even vary in time within one patient. Continuous assessment of CA may facilitate personalising blood pressure targets

which might result in improved outcome in aSAH patients.[93] However, as continuous assessment of CA is not yet feasible in most clinical practices, the best practical advice for the clinician treating aSAH patients at this moment would be to avoid MAP levels that are below the lower cerebral autoregulatory limit of 60 mmHg, and to be aware that individual patients may require individualised blood pressure targets. Whether avoiding a MAP of 60 mmHg or lower will actually prevent DCI should be further investigated and could be an interesting topic for future randomized trials.

PREVENTION OF DCI

Inflammation: antibiotic treatment to prevent DCI

Following the initial haemorrhage, infiltrating leucocytes are drawn to the subarachnoid space to start removing the extravascular blood.[94] As a result, inflammatory cytokines are released, inducing an inflammatory response which is associated with early brain injury[42,95,96], DCI[97,98] and poor outcome[99]. Several inflammatory cytokines, adhesion molecules, factors leading to platelet activation, leucocytes, fever and the presence of a systemic inflammatory response syndrome (SIRS) have all been linked to development of DCI and poor outcome. [52,100-113]

The prevalence of infection in aSAH patients, both in and outside the ICU, ranges from 26 to 41%[114] with the most common infections being pneumonia (17 – 20%) and urinary tract infections (9 – 13%)[115,116]. The presence of an infection during hospital stay was found to be an independent predictor of DCI in a recent prospective cohort study.[117] The authors elaborate that the presence of an infection leads to an enhanced inflammatory response, which in turn may lead to increased risk of DCI. In this study, the diagnosis of infection preceded the development of DCI in the majority (71%), but not all patients, and the authors suggest that further investigation is needed to define a causative relationship. However, it seems plausible that systemic inflammation, with or without the presence of an infection, is related to the development of DCI and might serve as a therapeutic target for preventing DCI and improving outcome.

We therefore investigated whether preventive antibiotics, through influencing infection and inflammation, were associated with a reduced risk of DCI and subsequently improved outcome in aSAH patients admitted to the intensive care unit (ICU) (**Chapter 4**[118]). Preventive antibiotics consisted of selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) which have been proven to reduce respiratory tract colonization with Gram-negative bacteria and to improve 28-day survival in a mixed population of ICU patients.[119] In our study consisting of 459 patients, we found

no association between the use of preventive antibiotics and the occurrence of DCI or poor outcome. The retrospective nature of the study, the presence of confounding by indication and the missing information on further use of antibiotics unfortunately prevented us from drawing firm conclusions.

The results of our study concur with large studies on preventive antibiotic treatment in patients with ischaemic stroke and intracerebral haemorrhage.[120,121] In the light of these studies, it might seem unlikely that preventive antibiotics will reduce mortality or poor outcome in aSAH patients. However, no other studies besides our own study have investigated the role of preventive antibiotics after aSAH. It is therefore too premature to state that preventive antibiotics are truly futile in reducing mortality or poor outcome after aSAH. Further, preferably prospective, studies are still needed to elucidate the role of preventive antibiotics in the management of aSAH patients.

Previous studies attempting to reduce the risk of DCI or poor outcome through anti-inflammatory strategies have shown varying results. Several different types and dose regimens of corticosteroids have been studied in aSAH patients with mixed results.[122,123] In the largest study (a retrospective cohort of 309 patients), dexamethasone significantly reduced the odds of unfavourable outcome, but it had no effect on DCI.[124] As this study lacked proper adjustment for possible confounders, it's results should be interpreted with caution. Immune suppressive treatment with cyclosporine A was investigated in two small studies. One randomised clinical trial of 25 patients showed improved outcome[125], the other smaller study showed a good safety profile but no effect on the development of DCI[126]. Statins have been studied extensively but a large randomised clinical trial showed no benefit in improving outcome at 6 months after aSAH or reduction of DCI.[127] The effect of non-steroidal anti-inflammatory drugs (NSAIDs) has been investigated in several studies. The results are again mixed, with two studies (one propensity-score matched study[128] and one randomised clinical trial[129]) showing no difference in functional outcome or the development of DCI or vasospasm, but another retrospective study suggesting improved outcome[130]. Several other anti-inflammatory and/or anti-thromboinflammatory treatment strategies (such as anti-platelet drugs and cilostazol) have been studied, all without proven beneficial clinical effects.[94,131,132]

To conclude, the role of anti-inflammatory agents has not been established and anti-inflammatory treatments are currently not recommended in aSAH. However, many of the investigated therapies have not been adequately studied and therefore definitive conclusions about their efficacy cannot be made. As it is plausible that inflammation with or without associated infection plays a role in the development of DCI and poor outcome, additional studies are needed to further determine the role of anti-inflammatory agents in improving outcome or preventing DCI in aSAH patients. As none of the abovementioned anti-inflammatory agents have shown consistent results, it is difficult to point out one

agent or strategy that seems most promising for further research. It seems better to focus first on becoming better in determining the most important contributing cause(s) of DCI in individual patients. Patients in whom inflammation or infection plays an important role in the development of DCI could serve as a properly selected group to investigate the effects of anti-inflammatory agents in. Neuro-monitoring might obtain an important role in determining the contributing causes for DCI in individual patients.

TREATMENT OF DCI: INDUCED HYPERTENSION

When DCI occurs despite preventive measures, the aim is to improve cerebral blood supply. In the presence of impaired CA and/or cerebral vasospasm, CBF becomes directly dependent on blood pressure. In 1976, Kosnik and Hunt were the first to describe resolution of clinical signs of DCI with intravenous fluids and induced hypertension in an observational, non-controlled study.[133] Shortly after, aggressive volume administration (hypervolaemia) to reverse signs of DCI was described.[134] Awad and colleagues eventually summarized these strategies as "Triple-H" therapy – hypertension, hypervolaemia and haemodilution – to improve cerebral perfusion.[135]

Of the three components of Triple-H therapy, hypervolaemia and haemodilution have fallen out of favor. Hypervolaemia proved to be non-beneficial and associated with more complications as opposed to normovolaemia[136-140], and haemodilution was found to actually decrease cerebral oxygen delivery despite increased CBF[141,142]. Further, in a systematic review, only induced hypertension seemed to increase CBF.[143] However, the effect of induced hypertension on CBF or outcome has never been investigated before in controlled studies let alone a randomised clinical trial.

Effect on cerebral perfusion

Therefore, we designed a randomised clinical trial (the HIMALAIA study) to investigate the effect of induced hypertension only as treatment for DCI, focusing on cerebral perfusion (**Chapter 6**[144]) and functional outcome (**Chapter 7**[145]). We found that induced hypertension did not improve overall CBF when assessed with CT perfusion (CTP). However, when we assessed changes in CBF in areas with lowest perfusion, we did find a trend towards improved CBF with induced hypertension.

We used CTP to measure cerebral perfusion as CTP is practical to use in daily practice and provides accurate estimation of cerebral blood flow in aSAH patients. Both decreased CBF and increased mean transit time (MTT) have been described in DCI.[146] However, even though perfusion measurements with CTP have been validated[147,148], exact quantification can be difficult. Various other studies have investigated the effect of induced hypertension

on cerebral perfusion. These studies vary in terms of how CBF was measured, when it was measured in relation to the intervention and which components of Triple-H therapy besides induced hypertension were used. The results are also heterogeneous. One study found that induced hypertension improved regional CBF and oxygen delivery measured with xenon-enhanced CT[140], another retrospective study found improved global CBF as reflected by elevated MTT on CTP[149], whereas a prospective positron emission tomography study found no effect on CBF or oxygen delivery in regions with low baseline CBF[150]. In a recent prospective study, cortical CBF was measured with repeated xenon-enhanced CT in 51 aSAH patients at day 0-3 and day 4-7 after aSAH. In 22 of 51 patients, triple-H therapy was used when clinical signs of DCI occurred. In these subjects, both global CBF and regional CBF in regions of the brain with worst perfusion increased significantly with Triple-H therapy.[151,152] However, this study was restricted only to patients that were intubated during the study measurements, it is unclear what the contribution of induced hypertension has been to this effect as the increase in blood pressure was small, and the two CBF measurements were separated by several days during which it is likely that other alterations in cerebral and systemic physiology (with or without the instalment of other interventions) occurred.

In conclusion, the existing literature including our own study does not provide sound evidence supporting the concept that induced hypertension produces a consistent and clinically meaningful rise in CBF. How then to explain clinical improvement that is observed in a proportion of patients receiving induced hypertension? First of all, clinical signs of DCI can vary in time independent of blood pressure or blood pressure augmentation. Improvement of clinical signs and the presence of higher blood pressure are in that case just a coincidence. Further, it might be that individual patients respond differently to induced hypertension. We have seen this in our own study where widely varying responses of CBF were seen after induction of hypertension, and this was also seen in another recent study consisting of poor grade aSAH patients, in which patients with previous low CBF showed a significant increase in CBF, whereas patients with initial high CBF showed no increase in CBF.[152] This varying response in alteration of CBF might be a reflection of differences in the extend of disturbance of cerebral autoregulation between patients. Therefore, assessment of individual limits of cerebral autoregulation and tailoring blood pressure to individual needs for optimal cerebral perfusion might be more important than just raising blood pressure[10]. A recent observational study in aSAH patients suggested that personalising blood pressure targets according to individually assessed limits of cerebral autoregulation resulted in better functional outcomes, and that exceeding individualized limits of autoregulation was associated with poor functional outcomes[93]. The most important (and yet unanswered) question however is, whether such personalized blood pressure targets would eventually lead to improved outcome in aSAH patients with DCI.

Effect on functional outcome

No randomised trials besides our own trial have investigated the effectiveness of induced hypertension on clinical outcome. As show in **Chapter 4** of this thesis, only 9 uncontrolled studies totalling 187 patients reported on clinical response to induced hypertension.[133,135,153-159] In these studies, improvement of neurological deficits ranged from 50 to 100%, with most studies reporting clinical improvement in around 80% of patients. In our own study, 57% of patients in de hypertension group showed clinical improvement which is in line with these previous findings.[145] The early clinical improvement after induced hypertension that is seen in a substantial percentage of patients may explain why induced hypertension is perceived and recommended as an effective treatment. However, it is still unclear whether this clinical improvement actually results in improved long term outcome. In 5 previous uncontrolled 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.[139,149,159-161] However, our trial showed that clinical improvement also occurred in patients who were not treated with induced hypertension, and that early clinical improvement does not always confer to a good outcome: of the patients that showed clinical improvement, 58% eventually had a good outcome in the hypertension group, as opposed to 100% of those patients in the no hypertension group.[145]
In summary, current literature including our own trial does not support the use of induced hypertension for improving functional outcome in DCI patients. However, the possibility of an effect on outcome, for instance in a certain selected subgroup of patients, cannot be ruled out as our study was underpowered due to the premature termination of the trial because of slow recruitment and lack of effect on cerebral perfusion.

Complications of induced hypertension

Induced hypertension is associated with systemic and intracerebral complications. In our own trial, 16 serious adverse events occurred in 41 patients, 11 (52%) in the hypertension group and 5 (25%) in the no hypertension group (risk ratio 2.1, 95%CI 0.9 – 5.0).[145] In the hypertension group, these complications included death (one probably related to induced hypertension), pneumothorax, atrial fibrillation, myocardial infarction and ECG changes necessitating halting the intervention. In other studies, serious complications occurred in 2% to as high as 49% of patients, including cardiac arrhythmia, pulmonary oedema, hyponatraemia, haemorrhagic transformation of cerebral infarction, posterior reversible encephalopathy syndrome (PRES) and intracranial bleeding.[135,139,153,155,157-159,162,163]

In most studies, including our own, raising blood pressure was kept at maximum levels, mostly MAP 120 to 130 mmHg and systolic blood pressure 220 to 230 mmHg, or MAP augmentation at 10 to 25% above baseline.[135,139,145,153,157,158] Patients with high baseline MAPs were excluded from triple-H or hypertensive therapy in several studies.[145,157]

However, in some studies, no absolute blood pressure thresholds were kept[155,163], or blood pressure thresholds were not documented[159]. A recent survey of blood pressure during induced hypertension confirmed that blood pressure regimens are quite variable, with centres setting no upper limits for blood pressure during induced hypertension, and centres keeping to predefined thresholds.[164]

Previous studies have suggested a relationship between the degree of therapy and the occurrence of complications. In one small study of 41 patients receiving normovolaemic induced hypertension, haemorrhagic complications (4 haemorrhagic infarctions, 3 haematoma's and 1 re-rupture of the aneurysm) were seen in 1 patient whose blood pressure was elevated with less than 25% above baseline, in 3 patients whose blood pressure was elevated between 25% to 50% above baseline, and in 4 patients whose blood pressure was elevated to more than 50% above baseline.[155] In another more recent study, PRES occurred more often in patients whose MAP was elevated above 140 mmHg or whose MAP was raised with more than 50 mmHg above baseline.[163] However, in this study, induced hypertension was accompanied by the use of hypervolaemia, and therefore it is unclear which component attributed most to the development of these complications.

Another unsolved question is whether different vasopressors have a different risk of complications. In one retrospective study comparing phenylephrine and norepinephrine, there was a suggestion of more complications with phenylephrine as compared to norepinephrine.[159] The authors suggest that this might be attributable to previous reports showing a dose-dependent reduction of cardiac output (CO) seen with phenylephrine as compared to norepinephrine.[165-168] A reduction in CO might result in decreased CBF, as a correlation between CO and CBF is reported in several studies in aSAH patients.[169,170] A more recent retrospective study showed an opposite result: phenylephrine was associated with reduced mortality in aSAH patients as compared to dopamine or norepinephrine.[171] An important limitation of this study was that a change of vasopressor occurred in 33% of patients during the same encounter of care, which was not accounted for in the statistical analysis. Dopamine is another vasopressor often used in studies investigating induced hypertension as treatment for DCI.[135,139,153,155-158] In one study, dopamine resulted in higher CO and cerebral oxygenation as compared to phenylephrine in patients undergoing cardiac surgery[172], but no such comparing report exist in patients with DCI after aSAH. Another unsolved issue is how the response to different vasopressors is in the setting of cardiac disturbances that are often seen in aSAH patients, including stress cardiomyopathy, systolic dysfunction[173], disturbances in pre- and afterload[174], and circulating catecholamines including norepinephrine[175].

As the efficacy of induced hypertension is not established and is associated with significant risk of serious complications, every clinician should carefully consider the indication for this therapy. When deciding to install the treatment, careful monitoring for cerebral and systemic adverse events seems equally important as careful instalment of the therapy.[176] Further, we suggest adjustment of recommendations in guidelines where induced hypertension is still recommended as Class I evidence.[70,177]

FUTURE PERSPECTIVES

Optimising prevention and treatment of DCI

To date, administration of nimodipine is the only way to reduce the risk of DCI after aSAH. However, the risk reduction is only 14%[65] and DCI still occurs in 20-30% of aSAH patients. We are thus still not able to effectively prevent or treat DCI in aSAH patients. The underlying reason is that DCI can occur as a result of many factors which also differ between patients. For instance, angiographic vasospasm might be the most important factor in one patient, whereas thrombo-inflammation might be the most important factor in another. Targeting angiographic vasospasm might help to prevent or treat DCI in the first patient, but will not be helpful in the other patient who might benefit more from an anti-thrombotic drug. This might be an important reason why previous studies (besides the nimodipine study) investigating numerous preventive or therapeutic measures in aSAH or DCI patients[13,132,178-180] came out negative or showed inconsistent results: one therapy might work for one or several patients, but probably not for all. In these previous studies, it is likely that some patients actually benefited from the treatment, but that this signal was lost due to insufficient power.

So how should we move forward? Besides providing specialised care for aSAH patients at dedicated neuro-medium or intensive care units, focussing on early aneurysm treatment, maintaining euvolaemia, preventing hypotension, preventing and treating infections and maintaining normal electrolyte levels[181,182], we need better options to optimise prevention and treatment of DCI. In order to do so, we will need to shift our strategies from uniform treatments to more personalised treatments. For personalised medicine to work in this group of patients, we have to become better in determining the most important contributing cause(s) of DCI in individual patients. Neuro-monitoring can become an important player in this field. Once we are better at determining individual causes for DCI, more targeted and tailored preventative or therapeutic strategies can be investigated in specific subgroup of patients. Current general measures as preventing hypotension or hypovolaemia might also be more successful when they are tailored to individual needs. For example, personalising blood pressure targets based on individually assessed limits

of cerebral autoregulation seem to result in better functional outcomes in aSAH patients whereas deviating from these personalized blood pressures was associated with worse outcome in these patients.[93] In line with this finding, perhaps induced hypertension as treatment of DCI might also be beneficial in an accurately selected subset of DCI patients.

Optimising research in DCI patients

As further research is much needed to find ways to prevent or treat DCI, how then should we conduct high quality research in these patients? As randomised clinical trials (RCTs) provide the best evidence for decision making about the clinical effectiveness of an intervention, this would be the preferred option. However, performing an RCT is very difficult in DCI patients as we demonstrated in our own trial (**Chapter 8)**.
As explained in Chapter 8, we feel that the small proportion of patients providing informed consent was the most important reason for the slow recruitment in our trial, and that this was mainly due to the complexity of our informed consent procedure. Various other informed consent procedures are discussed in Chapter 8, such as the 'deferred informed consent' method, the "Trials within Cohorts" (TWiCs) method[183,184] or the 'just-in-time' consent method[185]. However, with these methods, all or a proportion of patients are not beforehand informed about the study when there is actually plenty of time to do so as we have shown in our study. We feel that withholding this information is in our view not ethical and not in line with the honest and open communication that is part of the treatment, nor in line with current European guidelines.[186] Therefore, we would still advice the method that we have used for obtaining informed consent.

However, strategies to facilitate informed consent in this patient population should be explored. Although we aimed to deliver the trial information as clear as possible by using a compact informed consent document of 4 pages as opposed to a reported average length of 10 pages[187,188] and by providing additional verbal information and additional time to consider trial participation, this might still not have been clear enough especially for elderly patients or patients with limited literacy. Therefore, other ways of providing information might be more successful in transferring complex trial information, for instance through visual media such as short video's that patients or proxies can view in their own time. Previous studies have shown that video-assisted informed consent improves patients' understanding of the proposed treatment or intervention both in clinical practice as in research[189,190] and may result in faster enrolment with improved enrolment of minorities[191,192].

Another factor that hampers research in DCI patients is the fact that DCI can be difficult to diagnose, especially in patients with a poor clinical condition. In patients who can be monitored clinically, repeated neurological examination is the most accurate approach to detect DCI, as compared to CT-perfusion and transcranial Doppler ultrasonography.[193]

However, in aSAH patients who are in a poor clinical condition, early clinical signs of DCI can be difficult or impossible to detect. Timely and adequate diagnosis of DCI in these patients might be improved by using additional screening methods such as vascular imaging, continuous electroencephalography, transcranial doppler ultrasonography, brain perfusion imaging, and invasive brain multimodality monitoring.[194] However, all these methods have flaws.

Transcranial doppler ultrasonography and cerebral angiography are not sensitive enough as they detect macroscopic vasospasm which inadequately represents the underlying brain tissue perfusion at a microcirculatory level and does not directly translate to DCI.[195,196] Further, transcranial doppler ultrasonography can technically not be performed in 25% of patients and cerebral angiography is associated with a -albeit small- risk of cerebral infarction. Computed tomographic perfusion (CTP) is currently the most widely used method to study the microcirculation and local brain tissue perfusion[146,197] and is validated for perfusion measurements in aSAH patients[147]. CTP can further be used in the setting of clinical signs of DCI to detect DCI that is still reversible.[198] However, it cannot be used as continuous monitoring and differences in equipment and postprocessing methods cause a high degree of variability and warrant the need for standardized methods for measuring perfusion with CTP. Continuous electroencephalography (EEG) may predict DCI[199-201] and specific measures such as the alpha/delta ratio and alpha variability may allow for early detection of potentially reversible DCI which could guide treatment or inclusion in randomised trials[202,203]. However, the continuous real-time monitoring is laborious, and it is yet unclear which algorithm should be used for automated detection. In addition, EEG monitoring is insensitive to detect abnormalities in other areas than the brain convexity, complicating its use in standard clinical care and in clinical trials. Invasive brain multimodality monitoring (MMM) can detect early signs of cerebral compromise preceding cerebral ischaemia and serve as an early detection method for DCI and as a guidance for treatment.[199,204] However, measurements are only performed in a pre-chosen part of the brain risking missing other parts of the brain that are ischaemic.[205-207] Further, it is unclear which monitoring techniques should be included and several of the components are invasive and costly which requires expertise and complicates its implementation in standard clinical care and clinical trials. To summarize, screening methods might be of value in improving the detection of DCI in poor grade aSAH patients, but the downside of using these methods is that they are unpractical in clinical practice, and would complicate the implementation of a clinical trial.

Another important factor that can prevent successful completion of clinical trials in DCI patients is a physician driven factor. In the HIMALAIA trial, all members of the study team judged the trial to be clinically relevant and ethical. However, the personal beliefs of the other involved physicians about the efficacy of induced hypertension and institutional preferences may have influenced perception of clinical equipoise and subsequently may

have influenced recruitment. In one participating centre (the UMC Utrecht), induced hypertension was almost never used before the start of the trial, whereas in the other three centres, induced hypertension was used according to the preference and beliefs of the treating physician. Therefore, support for the trial amongst treating physicians may have been variable, which might have influenced alertness for the trial and willingness to consider their patients as trial candidates. In line with this factor of personal beliefs and preferences, we were unsuccessful in adding more national and international centres to the trial when inclusion proved to be slow.

Considering all the above mentioned factors, it is without doubt that completing a randomised clinical trial in DCI patients would require a tremendous effort. In the light of the difficult course of the HIMALAIA trial, it is questionable whether such a trial would be feasible. The complexities we encountered in the recruitment of patients are not unique[208] and any group wanting to attempt a new randomised trial in DCI patients should be well aware of these complexities and implement ways to overcome them as part of trial design[209].

To overcome the difficulties associated with designing a randomised controlled trial on treatment strategies in DCI patients, a different approach could be to use observational comparative effectiveness research (CER).[210] With CER, the effectiveness or safety of an intervention is evaluated in real-life practice by using data that are obtained during routine clinical care, aiming to determine which treatment will work for which patient. An important advantage is that data can be collected quickly and easier than in a randomised controlled trial. The major disadvantage is the risk of confounding by indication, which will inevitably prevent providing solid evidence based recommendations. As evidence based treatment strategies for DCI are much needed, we advocate improvement of randomised clinical trials in DCI patients.

Closing remarks

DCI after aSAH is undeniably complex, and the underlying mechanisms extend far beyond cerebral vasospasm. As the underlying mechanisms differ between individual DCI patients, it seems almost impossible to find a single solution that will benefit all. Future research should focus on improving detection of the major contributing causal factor in the development of DCI in individual patients, facilitating future clinical trials by selecting patient subgroups that are actually likely to respond to the more personalised intervention. As this will require large numbers of patients, the need for international collaboration and dedicated researchers and clinicians cannot be stressed enough.

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PART V

APPENDICES

Summary
&
Nederlandse samenvatting

SUMMARY

In this thesis we have examined potential risk factors for the development of delayed cerebral ischaemia (DCI), the use of preventive antibiotics to prevent DCI, and the efficacy of induced hypertension to treat DCI. With this focus, the aim was to find clinically applicable methods to better prevent or treat this serious complication after aneurysmal subarachnoid haemorrhage (aSAH) and to guide the design of future research as well as prevention and treatment strategies.

In **Chapter 2** we describe a cohort of 333 aSAH patients admitted to two university hospitals in the Netherlands. For each patient, the total haemorrhage volume after aSAH on non-contrast CT was quantified with an automatic quantification method that was previously developed and validated by the same study team. We found that a higher total haemorrhage volume and the presence of an intraventricular haemorrhage as measured with this method were both significantly associated with DCI.

In **Chapter 3**, we assessed the association between blood pressure and the development of DCI. We retrospectively retrieved the hourly validated blood pressure values for all consecutive aSAH patients admitted to the intensive care unit (ICU) of two centres in the Netherlands, and assessed whether they developed DCI during ICU admission or not. The cohort existed of 1167 aSAH patients of whom 110 (9%) developed DCI during ICU admission. We found a statistically significant association between a mean arterial pressure (MAP) of 60 mmHg or lower in the 24 hours preceding DCI, and the occurrence of DCI: the risk of DCI could become up to 2,6 times more likely with MAP of 60 mmHg or lower. For the current time, a practical advice to the clinician treating aSAH patients could be to try to avoid MAP values of 60 mmHg or lower. Whether a MAP of 60 mmHg or lower would actually prevent DCI should be further investigated in randomised trials.

As inflammation and infection are both associated with the development of DCI, we investigated in **Chapter 4** whether preventive antibiotics could lead to a decreased risk of DCI. In our retrospective cohort consisting of 459 consecutive aSAH patients admitted to the ICU of three university hospitals in the Netherlands, 274 patients (60%) received preventive antibiotics, and 185 (40%) did not. We found no association between the use of preventive antibiotics and DCI or poor outcome. These results concur with large studies on preventive antibiotic treatment in patients with ischaemic stroke and intracerebral haemorrhage. Therefore, it might seem unlikely that preventive antibiotics will reduce poor outcome in aSAH patients, also due to the fact that DCI is not only associated with inflammation but also with multiple other factors for which antibiotics will not be helpful. However, no other studies besides our own study have investigated the role of preventive antibiotics after aSAH. It is therefore too premature to state that preventive antibiotics

are truly futile in reducing poor outcome after aSAH, and further, preferably prospective, studies are still needed to elucidate the role of preventive antibiotics in the management of aSAH patients.

Induced hypertension is widely used to treat DCI but its presumed effectiveness was based on uncontrolled case series only. We set up a multicenter randomised clinical (the HIMALAIA study) in which we investigated the efficacy and safety of induced hypertension versus no induced hypertension as treatment for DCI.

Chapter 5 provides in detail the way the trial was set up, including the rationale for the trial, the in- and exclusion criteria for the trial, the endpoints of the trial, the sample size calculation, the statistical analysis and expected duration of the trial.

In **Chapter 6**, the results of the substudy on the effect of induced hypertension on cerebral perfusion as measured by CT perfusion are shown. This substudy involved 25 patients of whom 12 were treated with induced hypertension and 13 were not. Cerebral perfusion was measured as cerebral blood flow (CBF; ml/100g/second) in 12 predefined regions of interest. Even though the mean arterial pressure (MAP) was on average 12 mmHg (95% confidence interval 8.6 – 14.5) higher in the hypertension group than in the no hypertension group, there was no difference between the groups in the change of overall CBF or change of CBF in the lowest perfused region. Only in the hypertension group, there was a trend towards improved CBF after induced hypertension in the lowest perfused region.

The effects of induced hypertension on functional outcome are shown in **Chapter 7**. The trial aiming to include 240 patients was ended prematurely due to lack of effect on cerebral perfusion (**Chapter 6**) and slow recruitment when 41 patients had been randomised: 21 to induced hypertension and 20 to no induced hypertension. Induced hypertension did not result in improved functional outcome (adjusted risk ratio for poor outcome 1.0, 95% confidence interval 0.6-1.8) but showed a trend towards more serious complications such as atrial fibrillation, myocardial infarction and pneumothorax (risk ratio 2.1, 95% confidence interval 0.9 – 5.0). Due to the underpowered sample size, the results of our trial do not add evidence to support induced hypertension but do show that this treatment can lead to serious complications.

In **Chapter 8,** the reasons for the slow recruitment in the HIMALAIA study are investigated and discussed. The most important reasons were the large proportion of ineligible patients and the small proportion of eligible patients providing informed consent. We feel that an important reason for the latter was our rather complex informed consent procedure. Patients had to provide informed consent before the actual development of DCI so that randomisation would not be delayed at time of DCI and the quality of

informed consent would be guaranteed. However, patients and proxies often reported that they found it difficult to imagine whether they would want to participate *in case* DCI would develop. Our findings can be used for the design and for sample size calculations for future randomised trials. There is a need for improvement of the informed consent method and the selection of patients. Multicenter and multinational collaborations are essential to find better treatment options for patients with DCI.

NEDERLANDSE SAMENVATTING

Een aneurysmatische subarachnoïdale bloeding (aSAB) is een subtype beroerte waarbij een bloeding optreedt tussen de hersenvliezen (*subarachnoïdaal*) als gevolg van een gebarsten uitstulping (*aneurysma*) van één van de slagaders in de hersenen. Een aSAB komt veel minder vaak voor dan een herseninfarct of 'gewone' hersenbloeding, maar omdat het vaak jongere patiënten treft en geassocieerd is met een hoog sterftecijfer en hoge ziektelast is het effect op verlies van levensjaren net zo groot. Eén op de drie mensen die een aSAB krijgt overlijdt als gevolg van de ziekte, en van de mensen die de bloeding overleven kan slechts ongeveer de helft weer onafhankelijk functioneren. Daarnaast heeft het overgrote deel van de overlevers cognitieve en emotionele klachten en is werkhervatting vaak niet meer (volledig) mogelijk. Er zijn een aantal factoren die de kans op een slechte uitkomst na het doormaken van een aSAB vergroten. Dit zijn onder andere het doormaken van een herhaalde bloeding uit het aneurysma voordat het aneurysma kan worden behandeld (*recidief bloeding*), het ontwikkelen van een ophoping van vocht in de hersenvochtkamers (*hydrocephalus*) en het ontwikkelen van verlate hersenschade als gevolg van verminderd zuurstofaanbod, de zogenoemde *secundaire ischemie*.

Secundaire ischemie treedt op bij ongeveer 1 op 3 patiënten met een aSAB en wordt vooral gezien tussen de 3e en 21e dag na het optreden van de oorspronkelijke bloeding. Het is een ernstige complicatie: in patiënten die de initiële bloeding overleven is het optreden van secundaire ischemie de belangrijkste oorzaak van overlijden en ernstige ziektelast. Welke patiënten secundaire ischemie zullen krijgen is tot op heden nog niet accuraat te voorspellen, maar er zijn wel factoren die de kans erop verhogen, zoals een grotere hoeveelheid bloed op de eerste hersenscan (CT scan) en een slechte neurologische toestand bij opname in het ziekenhuis.

Symptomen van secundaire ischemie zijn nieuwe neurologische uitvalsverschijnselen, een dalend bewustzijn of een combinatie van beiden. Afhankelijk van de ernst van secundaire ischemie kunnen uiteindelijk herseninfarcten optreden die dan ook te zien zijn op beeldvorming van de hersenen (CT of MRI scan). Secundaire ischemie ontstaat als het zuurstofaanbod aan de hersenen (de bloedtoevoer) niet meer voldoet aan de zuurstof-vraag van het hersenweefsel. Het is inmiddels bekend dat verschillende factoren bijdragen aan het ontstaan van secundaire ischemie: vaatvernauwingen als gevolg van spasmen van de hersenbloedvaten (*cerebrale vasospasme*), stolselvorming in de kleine bloedvaatjes (*micro-trombo-embolisme*), het optreden van een ontstekingsreactie (*inflammatie*), veranderde elektrische ontlading van de hersencellen (*cortical spreading depression*) en gestoorde zelfregulatie van de bloeddoorstroming van de hersenen (*gestoorde cerebrale autoregulatie*).

Om het optreden van secundaire ischemie te voorkomen is het belangrijk om de bloedtoevoer naar de hersenen zo goed mogelijk te houden. Dit gebeurt onder andere door de bloeddruk op peil te houden en nimodipine voor te schrijven; het enige medicijn wat aantoonbaar het risico op secundaire ischemie verlaagt. Helaas treedt secundaire ischemie ondanks deze maatregelen alsnog op bij 20 tot 30% van de patiënten. Wetenschappelijk onderzoek heeft zich in de afgelopen decennia dan ook veelal gericht op het vinden van een (preventieve) behandeling voor secundaire ischemie.

In dit proefschrift zijn mogelijke risicofactoren voor het optreden van secundaire ischemie onderzocht, is de effectiviteit van een preventieve behandeling met antibiotica onderzocht en is de effectiviteit van therapeutische behandeling met een kunstmatig tot stand gebrachte hogere bloeddruk (*geïnduceerde hypertensie*) onderzocht. Het doel hiervan was om nieuwe methoden te vinden om deze ernstige complicatie te voorkomen of behandelen en om de totstandkoming van toekomstig wetenschappelijk onderzoek te faciliteren.

In **Hoofdstuk 2** beschrijven we een cohort van 333 aSAB-patiënten van 2 ziekenhuizen in Nederland. Voor elke patiënt werd de hoeveelheid bloed op de eerste CT scan (totaal bloedvolume) na de doorgemaakte SAB vastgesteld met behulp van een eerder gevalideerde geautomatiseerde meetmethode. We toonden aan dat een hoger totaal bloedvolume en de aanwezigheid van bloed in de vochtkamers van de hersenen (*intraventriculair*) samenhing met het optreden van secundaire ischemie. Verder onderzoek zal moeten aantonen of deze geautomatiseerde manier van meten bij kan dragen in het beter voorspellen van het optreden van secundaire ischemie.

In **Hoofdstuk 3** beoordeelden we of bepaalde bloeddrukwaardes voorafgaand aan het optreden van secundaire ischemie samen zouden hangen met een verhoogd risico op secundaire ischemie. We verzamelden retrospectief de elk uur gemeten bloeddrukken van alle achtereenvolgend opgenomen aSAB patiënten op de intensive care units (IC's) van twee ziekenhuizen in Nederland, en beoordeelden of ze secundaire ischemie ontwikkelden tijdens de IC opname. Het cohort bestond uit 1167 aSAB patiënten, waarvan 110 (9%) patiënten secundaire ischemie ontwikkelden op de IC. We vonden een significante relatie tussen een gemiddelde bloeddruk (*mean arterial pressure; MAP*) van 60 mmHg of lager in de 24 uur voorafgaand aan secundaire ischemie, en het krijgen van secundaire ischemie: de kans op secundaire ischemie kon wel 2,6 keer zo groot worden. Of het voorkómen van een MAP van 60 mmHg of lager daadwerkelijk leidt tot een verlaagde kans op secundaire ischemie zou verder moeten worden onderzocht in gerandomiseerde studies. Tot die tijd zou een praktisch advies aan de behandelend arts van aSAB patiënten kunnen zijn om een MAP van 60 mmHg als ondergrens aan te houden.

Omdat secundaire ischemie mede ontstaat door de aanwezigheid van inflammatie en infectie, onderzochten we in **Hoofdstuk 4** of het toedienen van preventieve antibiotica zou kunnen leiden tot een verlaagd risico op secundaire ischemie. Ook dit was een retrospectieve studie bestaande uit 459 aSAB-patiënten die waren opgenomen op de IC's van 3 ziekenhuizen in Nederland. Van de 459 patiënten kregen 274 patiënten (60%) preventieve antibiotica en 185 (40%) niet. Het toedienen van preventieve antibiotica leidde niet tot een verminderd optreden van secundaire ischemie. Als gevolg van de retrospectieve opmaak van de studie (*selectie bias, confounding by indication*) konden we geen zekere conclusies trekken. De resultaten van onze studie zijn echter wel in lijn met de resultaten van grote studies naar het effect van preventieve antibiotica bij patiënten met een herseninfarct of hersenbloeding. Het lijkt daarom onwaarschijnlijk dat preventieve antibiotica de uitkomst van aSAB patiënten zal verbeteren, ook omdat secundaire ischemie niet alleen samenhangt met inflammatie en infectie, maar ook met multipele andere factoren waarvoor preventieve antibiotica niet zullen helpen. Echter Echter, geen enkele andere studie buiten onze studie heeft de rol van preventieve antibiotica na het optreden van een aSAB onderzocht. Het is dan ook te vroeg om te beweren dat preventieve antibiotica zeker zinloos zijn in het verminderen van de kans op een slechte uitkomst na een aSAB. Aanvullend, bij voorkeur prospectief, onderzoek blijft dan ook gewenst om de rol van antibiotica bij de behandeling van patiënten met een aSAB te beoordelen.

Om de effectiviteit van een behandeling aan te tonen is het noodzakelijk deze behandeling te onderzoeken door middel van een gerandomiseerde studie: hierbij worden patiënten willekeurig 'geloot' voor de behandeling of niet zodat eerlijk en zonder invloed van verstorende factoren (bias) kan worden beoordeeld of de behandeling werkt. Geïnduceerde hypertensie wordt wereldwijd ingezet om secundaire ischemie te behandelen, ondanks dat de vermeende werkzaamheid nooit in een dergelijk onderzoek werd aangetoond. Om deze reden ontwikkelden wij een multicenter gerandomiseerde studie (de HIMALAIA studie) waarbij we de werkzaamheid en veiligheid van geïnduceerde hypertensie versus geen geïnduceerde hypertensie onderzochten als behandeling van secundaire ischemie.

In **Hoofdstuk 5** wordt gedetailleerd weergegeven hoe de studie was vormgegeven, inclusief de in- en exclusiecriteria voor patiënt-deelname aan de studie, de berekening van de studie-grootte, de eindpunten van de studie, de methode van statistische analyses en de verwachtte looptijd van de studie.

In **Hoofdstuk 6** beschrijven we de resultaten van de substudie naar het effect van geïnduceerde hypertensie op de bloedsdoorstroming van de hersenen (de *cerebrale perfusie*), welke we hebben gemeten met behulp van CT perfusie. Van de 25 patiënten werden er 12 behandeld met geïnduceerde hypertensie en 13 niet. De cerebrale perfusie

werd beoordeeld aan de hand van *cerebral blood flow* (CBF; ml/100g/seconde) in 12 vooraf vastgestelde regio's van de hersenen. Ondanks dat de gemiddelde bloeddruk hoger was in de hypertensiegroep dan in de niet hypertensie groep werd er tussen de groepen geen verschil gezien in de algehele cerebrale perfusie of in de perfusie van hersengebieden met de laagste cerebrale perfusie. Alleen binnen de hypertensie groep werd gezien dat de cerebrale perfusie neigde te verbeteren in het hersengebied met de minste perfusie na het starten van geïnduceerde hypertensie.

De effecten van geïnduceerde hypertensie op functionele uitkomst worden beschreven in **Hoofdstuk 7**. De studie die als doel had 240 patiënten te includeren, werd vroegtijdig beëindigd wegens gebrek aan effectiviteit in het verbeteren van de cerebrale perfusie (**Hoofdstuk 6**) en te langzame inclusiesnelheid, toen 41 patiënten waren geïncludeerd. Hiervan hadden 21 patiënten geïnduceerde hypertensie gehad en 20 patiënten niet. Geïnduceerde hypertensie leidde niet tot een verbeterde functionele uitkomst na 3 maanden maar neigde wel te leiden tot meer ernstige complicaties zoals myocard infarct, atriumfibrilleren en pneumothorax. Omdat in de studie te weinig patiënten waren geïncludeerd met als gevolg een onvoldoende onderscheidend vermogen (*power*) dragen de resultaten niet bij aan het ondersteunen van het gebruik van geïnduceerde hypertensie. Daarnaast lijkt de behandeling geassocieerd met meer ernstige complicaties.

In **Hoofdstuk 8** worden de redenen van de trage inclusiesnelheid in de HIMALAIA studie bediscussieerd. Een belangrijke reden was het grote deel van patiënten dat niet geschikt was voor deelname aan de studie. De andere belangrijke reden was het kleine deel van de geschikte patiënten dat toestemming (*informed consent*) gaf voor deelname aan de studie. Wij zijn van mening dat onze complexe informed consent procedure hier een belangrijke reden voor was. Patiënten moesten informed consent geven voorafgaand aan de daadwerkelijke ontwikkeling van secundaire ischemie zodat de daadwerkelijke randomisatie niet vertraagd zou worden op het moment van optreden van secundaire ischemie en om de kwaliteit van informed consent te behouden. Echter, patiënten en betrokkenen gaven vaak aan dat ze het moeilijk voor te stellen vonden of ze aan de studie mee zouden willen doen *in het geval* secundaire ischemie zou optreden.
De resultaten van de HIMALAIA studie kunnen worden gebruikt voor het ontwerpen van toekomstige studies en het maken van realistische berekeningen voor de benodigde grootte van dergelijke studies. De informed consent procedure zal moeten worden verbeterd, evenals de selectie van de juiste patiënten.
Om betere behandelopties voor patiënten met secundaire ischemie te kunnen vinden zijn internationale en multicenter samenwerkingen onontbeerlijk.

List of abbreviations

ADL:	Activities of daily living
AMC:	Amsterdam University Medical Center, location AMC
aSAH:	Aneurysmal subarachnoid haemorrhage
CA:	Cerebral autoregulation
CBF:	Cerebral blood flow
CER:	Comparative effectiveness research
CFQ:	Cognitive Failures Questionnaire
CI:	Confidence interval
CO:	Cardiac output
CPP:	Cerebral perfusion pressure
CSF:	Cerebral spinal fluid
CT:	Computed / computerised tomography
CTA:	Computed tomographic angiography
CTP:	Computed tomographic perfusion
CVC:	Central venous catheter
DCI:	Delayed cerebral ischaemia
DSMB:	Data safety monitoring board
DSA:	Digital subtraction angiography
EBI:	Early brain injury
ECG:	Electrocardiogram
EEG:	Electroencephalography
EMC:	Erasmus MC University Medical Center, Rotterdam
ETZ:	Elisabeth-Tweesteden Ziekenhuis Tilburg
HADS:	Hospital Anxiety and Depression Scale
HIMALAIA:	Hypertension Induction in the Management of AneurysmaL subArachnoid haemorrhage with secondary IschaemiA
(a)HR:	(adjusted) Hazard ratio
Hrs:	Hours
iHT:	Induced hypertension
ICH:	Intracerebral haematoma
ICP:	Intracranial pressure
IPH:	Intraparenchymal haematoma
IQR:	Interquartile range
ICU:	Intensive care unit
IVH:	Intraventricular haematoma / haemorrhage
mL:	Milliliter
MAP:	Mean arterial pressure
MMM:	Multimodality monitoring
MR(I):	Magnetic resonance (imaging)
MRA:	Magnetic resonance angiography

mRS:	Modified Rankin Scale
MTT:	Mean transit time
NCCT:	Non contrast computed tomography
NIHSS:	National Institutes of Health Stroke Scale
NSAIDs:	Non-steroidal anti-inflammatory drugs
(a)OR:	(adjusted) Odds ratio
PRES:	Posterior reversible encephalopathy syndrome
(a)RR:	(adjusted) Risk ratio
SAE:	Serious adverse events
SAH:	Subarachnoid haemorrhage
sBP:	Systolic blood pressure
SD:	Standard deviation
SDD:	Selective digestive tract decontamination
SIRS:	Systemic inflammatory response syndrome
SOD:	Selective oropharyngeal decontamination
SSQOL:	Stroke Specific Quality of Life Scale
TBV:	Total blood volume
Triple-H therapy:	Hypertension, hypervolaemia, haemodilution
UMCG:	University Medical Center Groningen
UMCU:	University Medical Center Utrecht
WFNS:	World Federation of Neurosurgical Societies

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List of publications

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1. Zijlstra IA, **Gathier CS**, Boers AM, Marquering HA, Slooter AJ, Velthuis BK, Coert BA, Verbaan D, van den Berg R, Rinkel GJ, Majoie CB. *Association of automatically quantified total blood volume after aneurysmal subarachnoid hemorrhage with delayed cerebral ischemia*. AJNR Am J Neuroradiol. 2016;37:1588-93.

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Curriculum vitae

Celine Sophia Gathier was born on June 3rd, 1985 in Dachau, Germany to Roel Gathier and Wilma Gathier-Leijten. At the age of 1, she moved back to The Netherlands with her parents, and grew up in Voorschoten with her brother Wouter and sister Anouk.

In 2003, she graduated with honors from secondary school (Stedelijk Gymnasium Leiden) and started medical school at Utrecht University. During medical school, she performed two scientific projects at the department of Neurology of the University Medical Center Utrecht (UMCU): the first on vasculitic neuropathy (supervisor dr. Alexander Vrancken), and the second on intracerebral haemorrhage (supervisor dr. Bart van der Worp), resulting in her first two publications.

After obtaining her medical degree in December 2009, she started her PhD on delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage in 2010, at the department of Intensive Care and the department of Neurology and Neurosurgery of the UMCU, (promotors: prof. dr. Gabriel Rinkel and prof. dr. Arjen Slooter). In that same year, she subsequently worked as a resident (ANIOS) at the department of Intensive Care and Neurology of the UMCU. She started the Neurology Residency program at the UMCU / St. Antonius Hospital in 2011 (supervisors: prof. dr. John Wokke, dr. Tatjana Seute, dr. Marjon van der Meulen), and performed an internship on neuro-oncology at the Amsterdam UMC, location VUmc and Antoni van Leeuwenhoek in 2018. From 2015 – 2019 she was a board member of the Vereniging Arts-Assistenten in opleiding tot Neuroloog (VAAN).

Currently, Celine is working as a neurologist at the Elisabeth-TweeSteden Ziekenhuis in Tilburg. She lives together with Pieter and their son Roel, and they are expecting a daughter in October 2020.