UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF

Klinik und Poliklinik für Neurochirurgie

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Safety and clinical effects of switching from i.v. to oral nimodipine administration in aneurysmal subarachnoid hemorrhage

Dissertation

zur Erlangung des Grades eines Doktors der Medizin an der Medizinischen Fakultät der Universität Hamburg.

vorgelegt von

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Hamburg 2022

Angenommen von der
Medizinischen Fakultät der Universität Hamburg am: 23.11.2023

Veröffentlicht mit Genehmigung der
Medizinischen Fakultät der Universität Hamburg.

Prüfungsausschuss, der/die Vorsitzende: Prof. Dr. Rainer Böger

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Original Paper: ***Göttsche J et al. Safety and Clinical Effects of Switching From Intravenous to Oral Nimodipine Administration in Aneurysma Subarachnoid Hemorrhage. Front Neurol. 2021 Nov 16;12:748413.***

Working assumption

Switching from intravenous to oral application of nimodipine for the prevention of cerebral vasospasm after aneurysmal subarachnoid hemorrhage is safe and has no effect neither on the rate and extent of cerebral vasospasm, delayed cerebral ischemia or cerebral infarctions.

Prologue

I hereby affirm that as a medical student and part of the working group around Göttsche et al. I have been significantly involved in data acquisation, data processing, interpretation of the results and finally drafting of the contents of the original paper `*Göttsche J, Schweingruber N, Groth JC, Gerloff C, Westphal M, Czorlich P. Safety and Clinical Effects of Switching From Intravenous to Oral Nimodipine Administration in Aneurysmal Subarachnoid Hemorrhage. Front Neurol. 2021 Nov 16;12:748413´*, which was basis for this dissertation in addition to my student project and could already be published in November 2021. I can therefore describe the contents as my own thoughts.

The original paper, which decisively led to this dissertation in addition to my student project, will be added at the end of the thesis.

1. Introduction

1.1. Thematic survey

This section on the `Thematic survey´ is part of the publication `*Safety and Clinical Effects of Switching from Intravenous to Oral Nimodipine Administration in Aneurysmal Subarachnoid Hemorrhage´* (Göttsche et al. 2021) and hence it will be referred to it.

Cerebral vasospasm and delayed cerebral ischemia (DCI) are further on severe and common complications after aneurysmal subarachnoid hemorrhage (SAH) and are altogether responsible for the high morbidity and mortality, which still amounts to over 20% in recent publications (Vergouwen et al. 2011, Petridis et al. 2017, Mader et al. 2020). Approximately 30% of all patients develop DCI during the course of aneurysmal SAH (Etminan et al. 2011). The pathophysiology underlying this is multifactorial in genesis: in addition to angiographic cerebral vasospasm, cortical spreading depolarization, microcirculatory dysfunction, micro thrombosis and neuroinflammation have recently been studied as factors effecting DCI (Rowland et al. 2012, de Oliveira Manoel et al. 2016, Francoeur and Mayer 2016, Geraghty and Testai 2017, Mohme et al. 2020, Göttsche et al. 2021).

Because repeated neurologic examinations cannot always be performed to assess clinical deterioration due to sedation or clouding of consciousness, transcranial Doppler sonography (TCD) is used as one of several methods to obtain evidence of cerebral vasospasm in the intracranial arteries (Kunze et al. 2012, Brami et al. 2020). TCD reflects the blood flow velocities in different intracranial arteries. An acceleration of velocities and flow disturbance correlates with local stenosis, hence giving

noninvasive insights of cerebral hemodynamics and emergence of cerebral vasospasm in case of aneurysmal SAH (Kumar et al. 2016, Djelilovic-Vranic et al. 2017, Samagh et al. 2019, Göttsche et al. 2021).

The calcium antagonist nimodipine has in several studies been shown to effectively reducing the incidence of severe neurologic deficits and poor outcome in the treatment of patients with aneurysmal SAH. However, nimodipine had no effect on the incidence of cerebral vasospasm or DCI. (Allen et al. 1983, Pickard et al. 1989, Trettenborn and Dycka 1990, Dorhout Mees et al. 2007, Göttsche et al. 2021). Calcium antagonists like nimodipine bind mainly to L-type voltage-gated Calcium (VGC) channels altering the influx of Calcium into smooth muscle cells, reducing peripheral resistance, why they are used as antihypertensive agents. Even though the underlying neuroprotective mechanism is not yet entirely understood, a positive effect on the functional outcome of patients has been confirmed (Roos et al. 2001, Al-Tamimi et al. 2010, Göttsche et al. 2021).

The Administration of nimodipine is meanwhile a well-established treatment regime and can happen intravenously (i.v.) or orally (Diringer and Zazulia 2017, Göttsche et al. 2021). Current guidelines recommend the oral application of nimodipine to all patients with subarachnoid hemorrhage (Connolly et al. 2012). However, there is evidence that through oral administration there is a lower bioavailability compared to intravenous administration, especially in patients with analgosedation (Abboud et al. 2015, Isse et al. 2020).

According to a recent retrospective analysis, less than 50% of all patients receiving oral nimodipine therapy received the full dose due to the antihypertensive effect of the drug, which should be avoided to prevent cerebral infarction (Sandow et al.

2016). This side effect of nimodipine counteracts the generally desired induced hypertension, often leading to intermittent suspension, decreased use or intravenous administration of norepinephrine (Trettenborn and Dycka 1990). Intravenous administration of nimodipine is a relevant alternative and has therefore been investigated in a whole series of studies in the past (Sramek et al. 1994, Soppy et al. 2012, Samseethong et al. 2018, Göttsche et al. 2021).

The aim of the analysis that led to this dissertation was to evaluate whether neurological and intensive care parameters change immediately due to the switch from i.v. to oral administration of nimodipine in the course of aneurysmal SAH with a special focus on the dosage of norepinephrine and the measured blood flow velocity in TCD (Göttsche et al. 2021). Significant differences in this field could be a basis for further investigations, since randomized data are not available at present.

The basics of aneurysmal SAH pathology, the development of cerebral vasospasm and the mechanisms of action of the calcium channel blocker nimodipine including the current controversies in the context of clinical application will be explained in detail. Furthermore, this thesis gives a brief overview of possible new therapeutic approaches against the background of current scientific findings, especially regarding the field of neuroimmunology.

1.2. Background on aneurysmal subarachnoid hemorrhage

1.2.1. Incidence and etiology of intracranial aneurysms

Main cause for the aneurysmal SAH is the spontaneous rupture of an intracranial aneurysm. The current literature suggests about 6 per 100,000 individuals per year

suffer from aneurysmal SAH and it is therefore a common occurrence in Emergency rooms worldwide. Regarding Europe this signifies a lethality of 35% (Etminan et al. 2020). The overall incidence of intracranial aneurysms is between 2% and 8% of the population (Sabouri et al. 2018).

Most commonly, ruptured aneurysms are located in the intracranial circulus arteriosus cerebri Willisii at typical sites such as the internal carotid artery (ACI) and at the junction of the anterior communicating artery (ACOM) and anterior cerebral

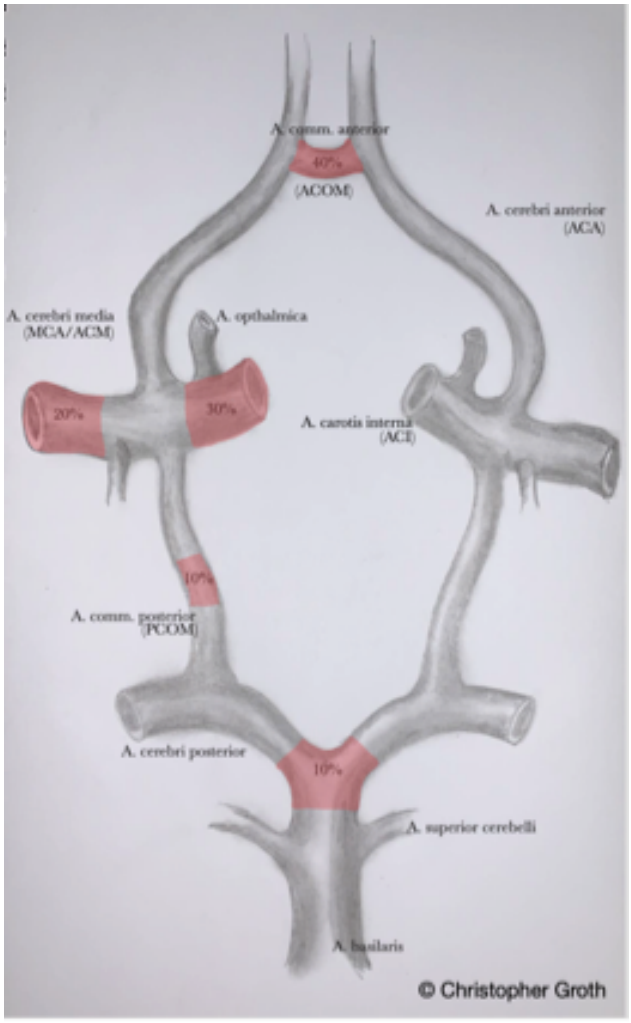

Figure 1: Occurrence of intracranial aneurysms

artery (ACA). Further predilection sites are the middle cerebral artery (MCA), the posterior communicating artery (PCOM) and the basilar artery (Diringer 2009), compare Figure 1.

The aneurysms can be subdivided in their morphology with a direct influence on the treatment method to be chosen for the treatment of the aneurysm (D'Souza 2015),

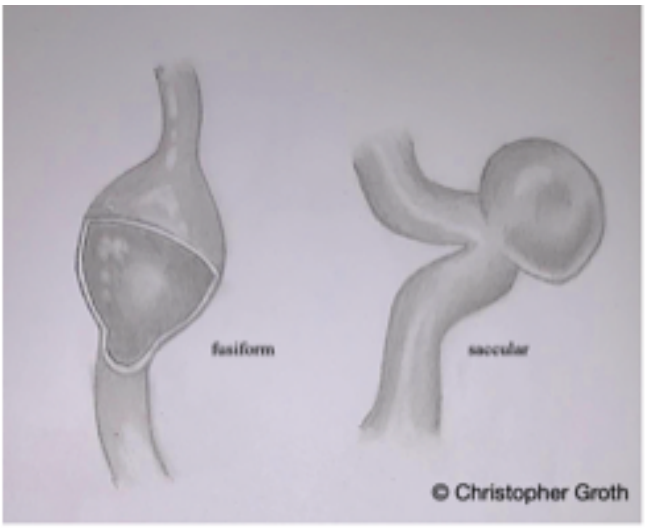

Figure 2: Morphological aspect of intracranial aneurysms

see also Figure 2. The processes that contribute to aneurysm formation act directly on the intracranial arterial vasculature system. Histologically, this often demonstrates a structurally thinned tunica media, or is preceded by a weak lamina muscularis (Shipman et al. 2019).

This structural degeneration in combination with hemodynamic stress, under the influence of known risk factors such as nicotine use, arterial hypertension, elevated cholesterol levels, excessive alcohol and drug use, or in the context of arteriosclerotic vascular change promote the development of an aneurysm (Schievink 1997a, Schievink 1997b).

Other risk factors relate to the sex or ethnicity of a patient. It is now known that both the female sex and patients who are of either Latino, Japanese, or African American

ethnicity have an increased likelihood of sustaining an aneurysmal SAH (Muehlschlegel 2018).

In recent years, the genetic component has gained importance as a theory in the development of aneurysms. Patients with an affected 1st generation family member also have an increased risk (8-10%) of developing an aneurysm (Nieuwkamp et al. 2009).

A 2013 meta-analysis also described that syndromal conditions, such as Marfan syndrome and Ehlers Danlos syndrome, may also imply a propensity to develop intracranial aneurysms (Murdoch et al. 1972, Alg et al. 2013, Brown and Broderick 2014).

Aneurysm formation on the basis of an inflammatory genesis as a hypothesis of origin, so-called mycotic aneurysms, on the other hand, is rather rare and lies in the single-digit percentage range. Risk factors are endocarditis, meningitis or cerebral abscesses (Schirmer 2005).

The exact pathophysiological mechanism of aneurysm rupture has not yet been clearly elucidated (Signorelli et al. 2018). The main causative factor is generally considered to be an increase in transmural pressure within the aneurysm. This is composed, on the one hand, of a decrease in cerebrospinal fluid (CSF) pressure and, on the other, of an increase in arterial blood pressure.

The systematic categorization of the rupture risk in intracranial aneurysms, including individual risk factors like age, clinical symptoms as well as morphology, location and maximum diameter of the aneurysm, has been the challenge for years (Mocco et al. 2018).

In 2015, Etminan et al. had been able to develop the first unruptured intracranial aneurysm treatment score (UIATS) and included the above-mentioned decisive points and facilitated the decision-making process in clinical treatment of unruptured intracranial aneurysms (UIA) (Etminan et al. 2015). A second score in order to predict the patient's individual 5-year risk of aneurysm rupture is the PHASES-Score which allows a comparison of the mortality and morbidity related with clinical intervention. Published in 2014 this score is still valid (Greving et al. 2014).

1.2.2. Clinical symptoms and classification of aneurysmal subarachnoid hemorrhage

The aneurysmal SAH mostly presents as an acute incident with a variety of symptoms implicating some major red flags such as strong hammer-like headache, neck stiffness and vigilance disorder. To predict the patients clinical outcome and evaluate the extent of the hemorrhage several scores are used in the clinical field. The Hunt and Hess grading system describes the clinical severeness of aneurysmal SAH (Hunt and Hess 1968), the distribution of the hemorrhage in the CT-scan is specified by the Fisher Scale (Fisher et al. 1980) - see also table 1 and 2.

The Fisher Scale can provide information about the risk for the occurrence of cerebral vasospasm based on computed tomographic findings. In the scientific field, the modified Fisher Scale is now increasingly used (Frontera et al. 2006). It is derived from the original Fisher classification. It should be noted, that the modified Fisher Scale includes on one hand the cisternal bleeding and accompanying intraventricular and intra-parenchymal bleeding components in the grading on the other (Frontera et al. 2006).

Table 1: Modified Fisher Scale

Degree	CT findings
0	No subarachnoid or intraventricular hemorrhage
1	Focal or diffuse SAH, thickness <1 mm, without intraventricular hemorrhage.
2	Focal or diffuse SAH, thickness <1 mm, with intraventricular hemorrhage.
3	Focal or diffuse SAH, thickness >1 mm, without intraventricular hemorrhage.
4	Focal or diffuse SAH, thickness >1 mm, with intraventricular hemorrhage.

Table 2: WFNS grading or Hunt and Hess Scale in relation to the Glasgow Coma Scale (GCS)

Degree	State of consciousness	Clinical symptoms	GCS
I	awake	asymptomatic or mild headache/ mild meningismus	15
II	awake	moderate to severe headache, meningismus, cranial nerve deficits	13-14
III	somnolence	minor neurological deficits, delayed response to pain stimuli	13-14
IV	sopor	moderate to severe focal neurological deficits, vegetative disorders	7-12
V	coma	sign of entrapment	3-6

In addition, the World Federation of Neurological Surgeons (WFNS) Score is applied in the clinical classification of aneurysmal SAH (Report of World Federation of Neurological Surgeons Committee 1988).

1.2.3. Therapy of aneurysmal subarachnoid hemorrhage

1.2.3.1. Diagnostics and initial management

In the systematic treatment of patients with aneurysmal SAH, several guidelines, including AHA and AWMF, have been developed in the last decades and further established under regular review of the study situation (Connolly et al. 2012, AWMF guideline). After diagnosis of aneurysmal SAH and endovascular or open microsurgical therapy, patients are usually undergoing an intensive care treatment with subsequent rehabilitation. Despite medical advances, a high mortality and morbidity rate remains associated with aneurysmal SAH (Nieuwkamp 2009). The immediate therapy onset is crucial as approximately 80% of patients suffer death or remain disabled in the long term (Roos 2000).

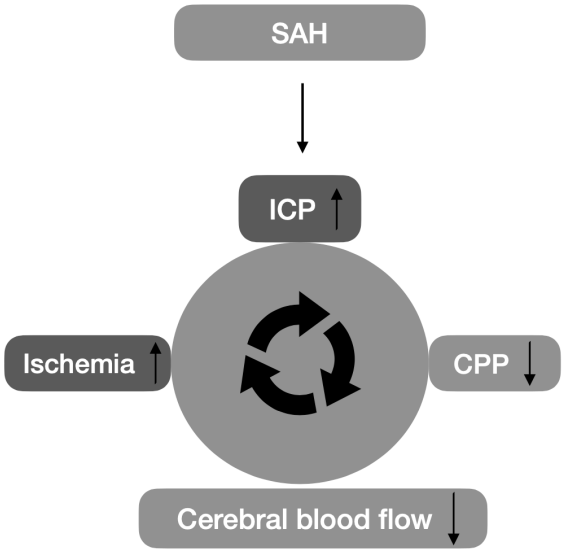

Figure 3: Diagram of the vicious circle of ICP, CPP, CBF and ischemia in the acute phase of aneurysmal SAH

Aneurysm rupture leads to an increase in intracranial pressure (ICP) within seconds or a few minutes and may reach the level of arterial pressure at its maximum. A vicious cycle of reduced cerebral perfusion, reduced cerebral blood flow (CBF), ischemia, and further increase in ICP can quickly occur hereafter, making aneurysmal SAH principally life threatening, compare Figure 3.

One sixth of affected patients die before reaching the emergency department (Petridis et al. 2017). Two thirds of patients reach the acute hospital in a reduced state of consciousness. This fact underscores the need for immediate initiation of further measures (Muehlschlegel 2018).

Time management is crucial. The time frame for therapy implementation in ruptured aneurysm is 72 hours after the initial hemorrhage (Molyneux et al. 2009). The implementation of neuroprotective measures is as well critical. These include, for example, monitoring of the mean arterial blood pressure, as well as upper body elevation (AWMF guideline). In hemodynamic therapy, a central venous pressure via central venous pressure (CVP) measurement of >4 mmHg and an arterial mean pressure >70 mmHg should be aimed for (AWMF guideline). Concerning diagnostical measures in aneurysmal SAH, native cranial computed tomography (cCT) is considered the gold standard due to its extremely favorable sensitivity of 95% within the first 24 hours after symptom onset. Magnetic resonance imaging (MRI) showed a sensitivity of 87% and specificity of 92% in some studies, but is consider a minor priority due to its lower availability (Greenberg 2010). In clinically conspicuous patients with an inconspicuous cCT, a lumbar puncture can be performed to confirm the diagnosis. A three-glass sample is taken to rule out iatrogenic blood involvement (AWMF guideline).

As a catheter-based technique, digital subtraction angiography (DSA) has become established in further diagnostics. It is particularly well suited to determine the possible source of bleeding as well as to assess the morphology of the aneurysm and the detection of already occurring cerebral vasospasm (Marcolini and Hine 2019).

1.2.3.2. Surgical therapy

The choice of intervention after confirmed aneurysmal SAH depends on various criteria, such as patient age, previous diseases, size and configuration of the aneurysm, and extent of bleeding. In principle, patients should be continuously monitored by intensive care until final aneurysm repair as well as after the intervention has been performed. In this way, possible complications in the course can also be detected early (Muehlschlegel 2018, AWMF guideline).

In most cases, the indication for open microsurgical or endovascular aneurysm treatment is based on DSA. The goal of the so-called microsurgical clipping is to separate the vascular bulge from the regular blood supply and initiate occlusion, which can be achieved in 90% of cases (Connolly 2010). Also, larger associated intracerebral hemorrhages can be evacuated surgically.

In a larger meta-analysis of 2460 patients, a mortality of 2 – 6% and a morbidity of almost 11% were shown in the context of this treatment (Raaymakers et al. 1998). In general, microsurgical clipping should be used in young patients (<50 years), without particular comorbidities and small aneurysms (<10 mm) in the anterior circulation (Ajiboye and Norman et al. 2015).

1.2.3.3. Endovascular therapy

Endovascular aneurysm coilembolization is another therapeutic option that has been known in Europe since 1992 (Molyneux et al. 2009). Coiling has gained importance in recent years, especially for non-ruptured aneurysms, however, the advantage in an acutely ruptured aneurysm, compared to microsurgical clipping is only marginal (Molyneux et al. 2009). The principle of coiling is to induce thrombosis of the

aneurysm with insertion of a coated coil (Greenberg 2010). Over the last years, this method was further developed and even complex and broad-necked aneurysms can nowadays be treated endovascularly. Via stent-assisted coiling, stents form a scaffold and thus prevent protrusion or dislocation of coils into the parent artery (Henkes et al. 2002).

Both the clip- and coil-provided aneurysm should be examined by prompt vascular imaging in the further clinical course and the success of therapy should be monitored. If stable occlusion of the aneurysm is demonstrated by MRA after approximately 6 months, the risk of aneurysm recurrence within the next 5 – 10 years is only approximately 1% (Ferns et al. 2011).

Lately, a new generation of devices has been established in endovascular therapy. The flow-diverter device and the woven endo-bridge (WEB) device are used in cases of particularly complex aneurysm morphology and unfavorable location at vessel bifurcations (Armoiry et al. 2015). The goal of these devices is to interrupt intraaneurysmal blood flow and induce occlusion by altering the transmural pressure gradient (Briganti et al. 2015). In 2015, Armoiry et al. studied the occlusion rate of the WEB device. It ranged from 65% to 85.4% with medium-term follow-up period of 3.3 – 27.4 months (Armoiry et al. 2015). In contrast, the occlusion rate of the Flow-Diverter Device is about 75% within 6 months (Akgul et al. 2016).

1.2.4. Complications after aneurysmal subarachnoid hemorrhage and their clinical management

In the period of intensive care therapy, various complications can occur during, pitfalls that are making the treatment of the aneurysmal SAH patients so challenging. Complications, such as cerebrospinal fluid circulation disorders, problems with long-term ventilation, cardiac effects and, in particular, cerebral vasospasm and, as a consequence, cerebral ischemia. In this context, the development of cerebral vasospasm should be seen as a complex, multifactorial event, which is the subject of current scientific efforts (Diringer et al. 2011).

Arterial hypertension is as well as the size of the aneurysm a risk factor for rebleeding from the ruptured aneurysm. The mortality rate in this case is 20 – 60%. This makes rebleeding one of the most feared complications of aneurysmal SAH. On average, 15% of patients with aneurysmal SAH experience rebleeding during the first few hours (Van Gijn et al. 2007). The majority of these rebleeds occur in the first 6 hours after aneurysm rupture (Lantigua et al. 2015).

Approximately 67% of all aneurysmal SAH patients develop symptomatic hydrocephalus during the acute phase; a risk that increases with the patient's age (Greenberg 2010, AWMF guideline). This typically malresorptive hydrocephalus develops in the context of malresorption at the arachnoid granulations within the CSF system due to the presence of blood degradation products (Siddiqi 2008). In this regard, the location of the ruptured aneurysm may play a role. For example, SAH from an MCA aneurysm correlates with a lower incidence of hydrocephalus (Graff-Radford et al. 1989).

The primary therapy approach for hydrocephalus is the installation of an external ventricular drainage (EVD) or lumbar drainage (LD). The goal is to achieve prompt clearance of the CSF and to allow normalized CSF circulation. EVD is replaced by a permanent ventriculo-peritoneal shunt in the course if CSF circulation disturbance persists (Hasan et al. 1989, Mohadjer et al. 1999). In addition to the development of hydrocephalus, the development of cerebral vasospasm is a major complication after aneurysmal SAH - this will be the focus of further discussion.

1.3. Principles of Transcranial Doppler sonography and its role in aneurysmal subarachnoid hemorrhage

The TCD has been the most important real-time, radiation free, noninvasive tool on ICU in order to detect cerebral vasospasm and monitor the patients' intracranial hemodynamics. It provides inexpensive real-time flow velocity of the main cerebral arteries and therefore detects focal vascular stenosis or sign of cerebral vasospasm (Purkayastha and Sorond 2012). The foundation of the TCD is laid by the principles of the known doppler effect, first indicated by Christian Doppler in 1842 (Pinter 2011).

While traveling through the vascular system the erythrocytes are forming the laminar blood-flow. Due to this principal the red blood cells are reflecting or scattering the impinging ultra sound waves in the intracerebral vessels, which results in a frequency change (MHz) as a measurable parameter (DeWitt and Wechsler 1988, Purkayastha and Sorond 2012).

Specifically, the analyzed parameters are the peak systolic velocity, end diastolic velocity, systolic acceleration time, pulsatility index and the time-averaged mean maximum velocity (Vmean) (Tegeler and Ratanakorn 1999) which we defined as

parameter in our examinations. As the blood-flow velocity is a flexible variable it can be affected by a number of physiologic factors such as age, gender, temperature, blood pressure, carbon dioxide level (Arnolds and von Reuter 1986, Grolimund and Seiler 1988, Vries et al. 1989).

1.3.1. The Transcranial Doppler sonography examination

Through different acoustic windows it is possible to examine different skull regions and their vessels using a 2MHz frequency ultrasound probe (DeWitt and Wechsler 1988, Aaslid 1986). The spreading of the ultrasound wave is constant, but accurate measure of flow velocity is depending on the performed angle, the examiner's experience and equipment type. Specific arteries of the circle of Willis can be identified using the transtemporal window (compare Figure 4).

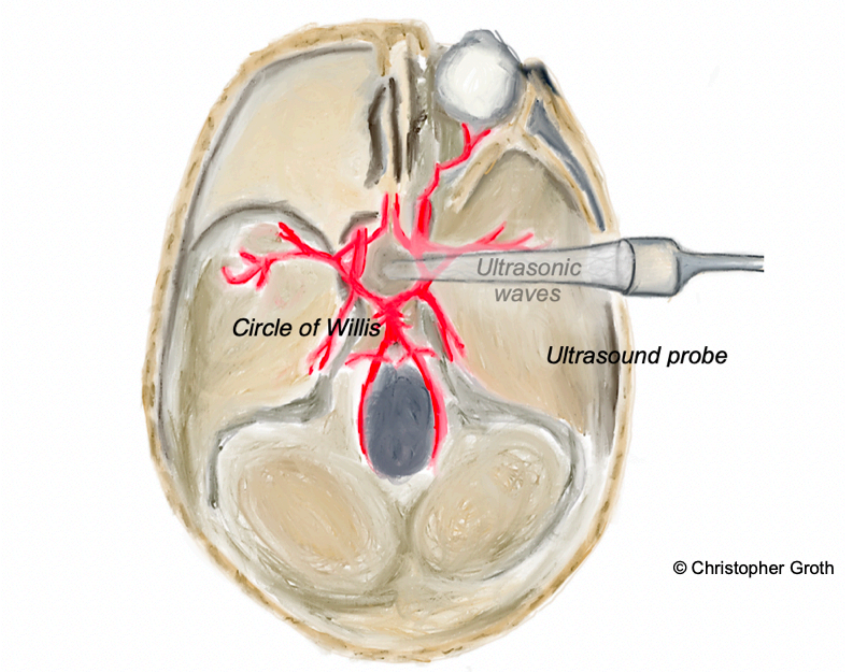

Figure 4: Schematic representation of TCD of the Circle of Willis

Here, the intracranial carotid artery (ICA) bifurcation can be identified at depths of 55-65mm. The MCA, viewed at depths of 35-55mm, runs laterally and slightly anterior

after its origin from the ICA. The ACA is to be found in 60-70mm depth, compare table 3 (Aaslid 1986, Ringelstein et al. 1990).

Table 3: Standard values TCD examination

Window	Vessel	Depth (mm)	mFV (cm/s)
Temporal	MCA (M1)	35-55	45-75
	ACA (A1)	60-70	40-60
	PCA (P1)	60-75	30-50
Submandibular	ICA	55-65	25-45

mFV: mean flow velocity

1.3.2. Limitations of Transcranial Doppler sonography

The standard TCD procedure screens the supratentorial arteries and the basilar artery because of their detection accessibility and specification in cerebral vasospasm diagnostic (Bonow 2019, Neulen et al. 2020). Due to some limitations TCD examination should be understood as an index of global rather than local cerebral blood flow velocity. The method is highly examiner dependent who should provide a full knowledge of cerebrovascular anatomy and its variations. The other important factor of possible results falsification is patient movement during the TCD procedure (Neulen et al. 2020).

Therefore, in our study TCD examinations were mainly performed by a proven medical technical assistant (MTA) to assure a comparability of our data. Yet, the implementation is prone to inaccuracies.

Another limitation of the TCD is the 10 – 15% rate of inadequate acoustic windows common in elderly women, Asians or Afro-American people possibly related to thickness and porosity of the bone that could weaken the ultrasound energy transmission (Purkayastha and Sorond 2012). Neulen et al. were able to include the image-guided TCD to infratentorial arteries in TCD examinations of cerebral vasospasm after SAH. The technique used in the study could be applied to improve the precision TCD examination (Neulen et al. 2020).

1.4. Aspects of cerebral vasoreactivity and autoregulation

The CBF is the central control mechanism for supplying the human brain with necessary metabolites. It is dependent on the intrinsic ability of smooth muscle cells to tense and relax to avoid major fluctuations (Meng et al. 2015). The networks among venous endothelial cells, smooth muscle cells, pericytes, astrocytes and perivascular neurons communicate via pathways of arachidonic acid metabolites released from phospholopase A2 resulting in depolarization of smooth muscles and vasoconstriction (Xiao et al. 2017).

All these factors can in advance reduce the ability to autoregulate and decrease CBF. Despite the sophisticated mechanism of autoregulation, the brain needs 12% of the cardiac output (Meng et al. 2015). It is common consensus that as long as the blood pressure fluctuates only to a limited extent within the autoregulation range the CBF would not be affected.

However, studies have shown that any form of alteration in cardiac output, be it acute, like aneurysmal SAH or intracranial hemorrhage (ICH) or chronic, like chronic heart failure, can lead to a notable change in CBF (Meng et al. 2015). Fluctuations in

the autoregulatory range are rather counterproductive at particularly low CBF values and lead to autoregulation failure and blood congestion and might be seen as harbingers of vasospasm (Sioutos et al. 1995).

1.5. Development of cerebral vasospasm

Two thirds of patients who are sustaining an aneurysmal SAH tend to develop cerebral vasospasm within the first 4 – 14 days (Bracard and Schmitt 2008, Bar et al. 2015). An individual risk assessment for the occurrence of cerebral vasospasm has been introduced by Jennifer Frontera, in 2006, the modified Fisher Scale (Frontera et al. 2006). In 2012, there was an attempt by the Barrow Neurological Institute (BNI) to reliably predict the risk of cerebral vasospasm by using a new classification and introducing new parameters, such as the thickness of the clot in the subarachnoid space. The study included 250 patients. According to the authors, the BNI-classification was superior to the Fisher Scale without mentioning a comparison to with the modified Fisher Scale (Wilson et al. 2012). Implementation into clinical practice did not occur due to the small cohort size.

Basically, when assessing risk, neither a higher patient age nor arterial hypertension in patient history in combination with antifibrinolytics and high Hunt and Hess grade increase the risk of developing cerebral vasospasm in the vulnerable phase after aneurysmal SAH (Adams et al. 1987, Macdonald et al. 2003).

The vulnerable group of patients, often present with increasing disorientation and agitation, focal neurological deficits to increasing loss of consciousness (Greenberg 2010, Purkayastha and Sorond 2012).

Cerebral vasospasm can be suspected in the clinical setting by clinical examination and diagnosed by TCD as well as CT angiography and digital subtraction angiography (Bonow et al. 2019). In this context, TCD is available directly at the patient's bedside and can ensure proper timing of therapeutic and angiographic interventions. Flow accelerations above the MCA of $V_{mean} \geq 140$cm/s measured by TCD, as well as an abrupt increase in V mean of > 65cm/s or 20% within a day, indicate cerebral vasospasm or increased ICP requiring further therapeutic intervention (Majewska et al. 2021).

The influence of physiologic changes on blood flow velocity or pulsatility should always be interpreted in correlation with the patient's condition and in the context of other variables that may affect flow velocity. These include individual anatomy, patient age, ICP, mean arterial pressure (MAP), potential technical problems, hematocrit, arterial CO2 level, and other therapeutic interventions (Sloan et al. 2004, Saqqur et al. 2007). It is important for the treatment of cerebral vasospasm to take a closer look at the multifactorial mechanism of origin and its causes.

1.5.1. Physiology of vascular muscle contraction

Cerebral vasospasm is the result of involuntary smooth muscle contraction in the tunica media (Koide et al. 2002). Smooth muscle contraction is based on the well-studied and well-known mechanism of muscle contraction and is essentially the same as muscle contraction in striated muscle (Hilgers and Webb 2005).

In a healthy human, stimulus conduction is triggered by depolarization of the smooth muscle cell and its membrane. Initially, the action potential is triggered by the activation of the stretch-independent ion channels. At the same time, the voltage-

gated calcium channels located in the plasma membrane are activated (Hilgers and Webb 2005).

In healthy individuals, this calcium-dependent, electromechanically coupled process leads to cross-linking between the actin and myosin filaments via phosphorylation of adenosine triphosphate (ATP). This cross-linking results in a shortening of the (heavy) actin and (light) myosin chains and, consecutively, in the twofold tilting of the myosin head (90° to 45°) and contraction of the muscle (Behrends et al. 2016).

The contraction results in an intracellular increase in calcium concentration. However, a high calcium concentration can also be established inside the cell by other means, e.g. pharmacological or hormonal and by autocrine/paracrine transductionn (Behrends et al. 2016).

Various autocrine/paracrine messengers, such as norepinephrine or endothelin-1, bind to the binding domain, the so-called heterotrimer, of the cell membrane of the smooth muscle cell (Hilgers and Webb 2005). This binding activates the so-called phospholipase C in the first step. Subsequent stimulus transmission occurs via stimulation of phosphatidylinositol-4,5-biphosphate, which in turn initiates the formation of inositol-1,4,5-trisphosphate and the second messenger diacylglycerol (DAG). DAG is responsible for the activation of protein kinase C (PKC) in the further cascade; a kinase that is later crucially required for the phosphorylation of certain target proteins. PKC exhibits a potent contraction-promoting effect (Koide et al. 2002, Hilgers and Webb 2005), compare Figure 5.

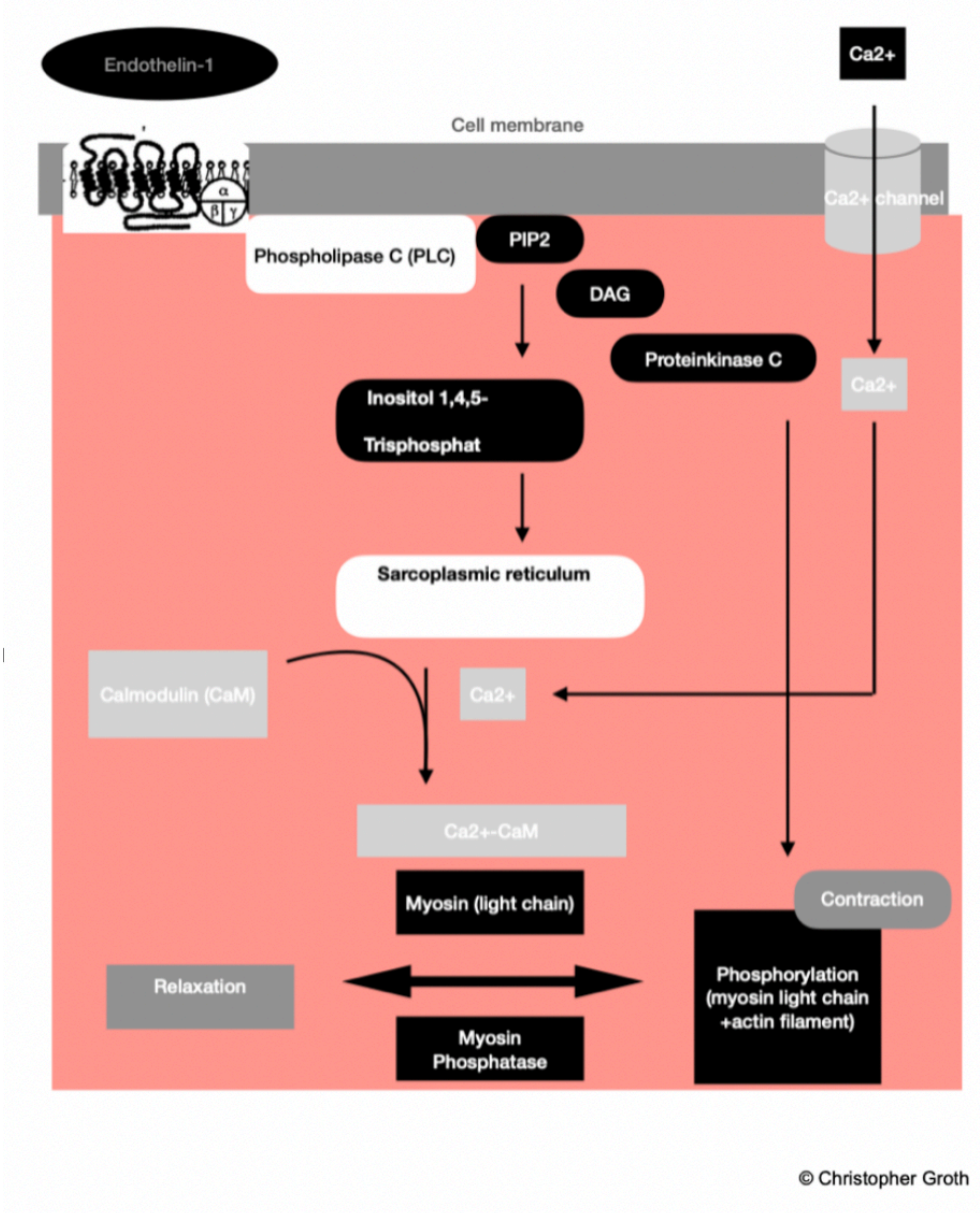

Figure 5: Schematic representation of the mechanism of vasoconstriction on the smooth muscle cell

Decisive for the subsequent vasodilation after the muscle contraction is a relaxation of the vascular smooth muscle due to a decrease in the intracellular calcium level. This physiological process is supported by antiporters, which transport calcium into the extracellular space with the highest possible temporal efficiency (Hilgers and Webb 2005).

In contrast to cerebral vasospasm, physiological muscle contraction involves both adequate calcium levels in the myofibrils and undisturbed calcium flow, which enters cells via voltage-gated and receptor-gated calcium channels (Koide et al. 2002).

1.5.2. Pathophysiology of cerebral vasospasm

Cerebral vasospasm occurs more frequently during a critical period of 4-14 days after aneurysmal SAH (Tsivgoulis et al. 2009). In the case of cerebral vasospasm, recent studies provide evidence for an evolving automatism between proteins and calcium channels of vascular muscle cells. This is triggered by oxidative stress within the subarachnoid space, which leads finally to an increased activity of L-type VGC channels (Pluta et al. 2009). This automatism thus equally affects intra-extracellular signal transduction, leading to increasing functional impairment of the affected vascular segments (Koide et al. 2002).

Another interesting factor in the formation of cerebral vasospasm is the dysfunction of NO (nitric oxide) synthetase. NO is known to be a potent vasodilator and is critical for the regulation of muscle tone. Studies have demonstrated failure of NO synthetase in vessels with cerebral vasospasm (Pluta et al. 2005).

A prolonged situation of cerebral vasospasm often ends with permanent damage to the endothelium due to loss of NO synthesis capacity (Koide et al. 2002). This loss of function of the cerebral vessels to regulate contraction, in combination with the existing cerebral vasospasm and perfusion reduction, can lead to DCI (Francoeur and Mayer 2016).

1.6. Clinical significance of cerebral vasospasm

A so far understood multifactorial pathophysiology including cerebral vasospasm after aneurysmal SAH implies DCI and involves a poor clinical outcome (Geraghty and Testai 2017). In two thirds of patients suffering from aneurysmal SAH angiographic cerebral vasospasm are detectable, whereby about 50 percent do not show any symptoms (Purkayastha and Sorond 2012). Findings of MCA V_{mean} ≥ 180 cm/s measured via TCD as well as an abrupt rise in MCA V_{mean} by > 65 cm/s or 20% within one day during posthemorrhage days 3 to 7 suggests cerebral vasospasm or increased ICP requiring interventional therapy (Tsivgoulis et al. 2009). TCD is useful in monitoring cerebral vasospasm after aneurysmal SAH assure right timing of diagnostic and therapeutic angiographic interventions. Certainly, sporadic TCD measurements, especially initiated after the occurrence of cerebral vasospasm, seem less sensible (Purkayastha and Sorond 2012).

The DSA is widely accessible and its reliability in the imaging of the vascular system ensures an important role in the detection of cerebral vasospasm. Yet it could be shown earlier, that CT angiography (CTA) is as well adequate to detect cerebral vasospasm, digital cerebral subtraction angiography is gold standard to intervene regarding lysis or angioplasty (Shankar et al. 2012).

It could be discussed, whether a routinely performed assessment algorithm during ICU therapy via TCD measurement in patients after aneurysmal SAH can be standardized and lead to earlier transmission of the patient to non-ICU ward in case the patients' condition otherwise allows it and nimodipine application is already switched to an oral one, compare Figure 6.

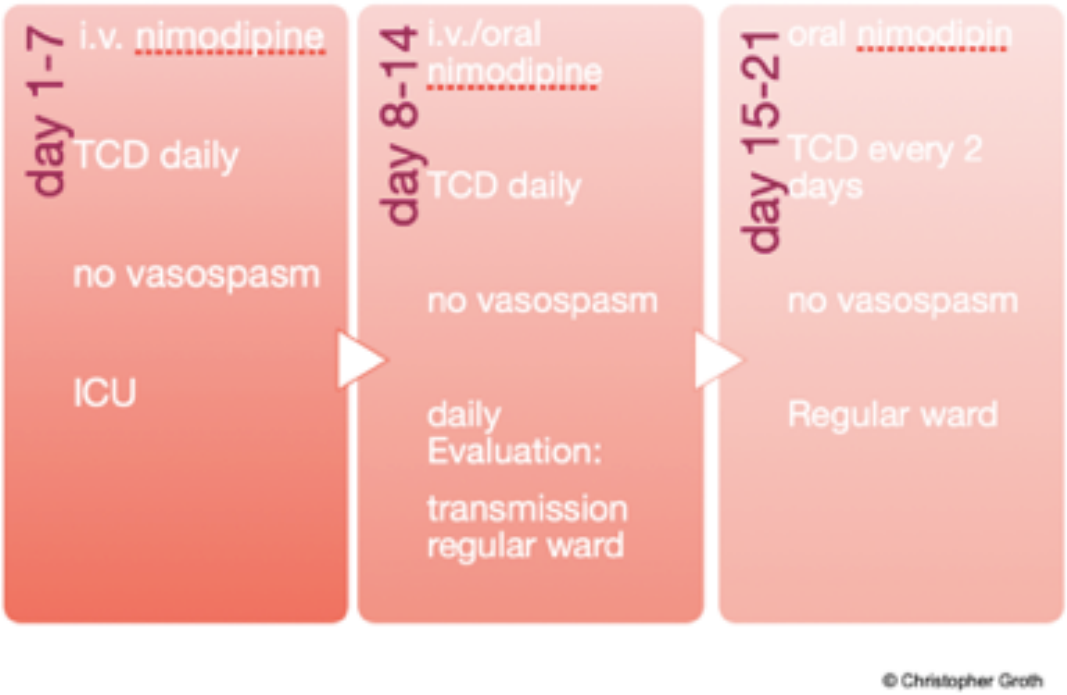

Figure 6: Suggested TCD assessment algorithm while nimodipine application due to aSAH

1.7. Delayed cerebral ischemia

Since 2010, DCI is defined as “the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (GCS) (either on the total score or on one of its individual components). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies” according to Vergouwen et al. 2010 in *Stroke* (Vergouwen et al. 2010).

The development of DCI in the context of cerebral vasospasm has a multifactorial genesis and the pathomechanism is the subject of current research (Rowland et al. 2012). The so-called early brain injuries, such as loss of function of the endothelium,

neuroinflammation with consecutive edema formation, loss of conduction autonomy due to cortical spreading depolarization (CSD) as well as loss of cerebral autoregulation are considered as possible influencing factors (Rowland et al. 2012, Budohoski et al. 2014, Foreman 2016, Geraghty and Testai 2017).

The DCI should be understood as a possible direct consequence of cerebral vasospasm and occurs on average in 30 – 40% of patients after aneurysmal SAH (Budohoski et al. 2014). It remains one of the most feared secondary complications with its high mortality and worsening outcome (Darkwah et al. 2019).

One primary tool for monitoring and detecting DCI in real-time is brain perfusion imaging (BPI). Another method of imaging cerebral perfusion that has gained increasing attention in recent years is computed tomographic perfusion imaging. By this method, conclusions can be drawn about the presence of cerebral vasospasm, but a prediction of certain occurrence of cerebral vasospasm by this method is not established yet. It remains to be clarified what clinical advantage this method has in terms of mortality and direct patient outcome (Cremers et al. 2014).

1.8. Neuroinflammation - immunological aspects related to cerebral vasospasm

In the recent years, several scientific groups have increasingly focused on the topic of inflammatory events following DCI after aneurysmal SAH and their role in the development of secondary brain injury (Ciurea et al. 2013). Further investigations recently focused on mechanisms of early brain injury relating to the patients outcome, such as neuroinflammation and microvascular dysfunction. Blood in the subarachnoid space after aneurysm rupture causes inflammatory response by activation of microglia. This results in impaired neurovascular coupling and

imbalances in endogenous vasoconstrictors and vasodilatators. Each process is either directly or indirectly associated with neuronal death and brain injury (Geraghty et al. 2019).

It is known that inflammation can aggravate cerebral vasospasm because of the pro-inflammatory effect of cytokines and chemokine inflammatory events in the subarachnoid space can be roughly divided into the two groups of cellular inflammation and molecular inflammation (Vecchione et al. 2009). After aneurysm rupture, blood enters the subarachnoid space. The released blood components, such as hemoglobin and haptoglobin, are seen by the immune system as harmful metabolites. The metabolites are triggering an immune reaction which includes attraction and deposition of neutrophil granulocytes and macrophages on the endothelium of the cerebral vessels (Lucke-Wold et al. 2016).

Activation of glial cells triggered by the increase in ICP, in cooperation with hypoperfusion, amplifies pre-existing endothelial dysfunction and leads to intrathecal activation of proinflammatory immune cells, regulatory T cells, and expression of adhesion molecules, so-called CAMs (Pradilla et al. 2010, Sehba et al. 2012, Mohme et al. 2020).

Cytokines and chemokines in particular, but also proinflammatory mediator substances such as TNF alpha and the adhesion protein (integrin) ICAM-1, which is crucial in leukodiapedesis, were detected. These integrins are released by inflammatory cells in association with other chemokines and cytokines, such as IL-1β, IL-6, IL- 8, and are considered to promote vasospasm (Gaetani et al. 1998, Provencio et al. 2010). In 2003, McGirt et al. were able to demonstrate a correlation

between an increased number of leukocytes in the peripheral blood and the development of cerebral vasospasm (McGirt et al. 2003).

The role of CSF in the development and spread of inflammation in the subarachnoid space is the subject of current research. However, to date, studies have already demonstrated the presence of the aforementioned immune cells, cytokines, and adhesion molecules (CAMs) in CSF (Provencio et al. 2010, Mohme et al. 2020).

Within the first days after aneurysmal SAH, the immune cells detected in CSF are not only limited to neutrophil granulocytes and proinflammatory factors. Followed by neutrophil recruitment at the vessel wall it is understood as the cause for the cerebral scattering of the inflammation with its peak after 14-28 days. It is important to note that cells of the adaptive immune system (T-cells and B-cells) are hardly represented in the CSF during the first 7 days (Mathiesen and Lefvert 1996, Provencio 2013). In contrast, a higher number of neutrophil and natural killer cells as well as monocytes, and macrophages can be detected. Special interest pertains to the molecular components that are detectable in CSF after hemorrhage and which may influence or aggravate the occurrence of cerebral vasospasm. It had been shown that especially the detection of IL-6, IL-1R antagonist and TNF alpha in CSF clearly correlate with a poor clinical outcome of the patient (Mathiesen et al. 1993, Mathiesen and Lefvert 1996, Mathiesen et al. 1997).

In 2020, Mohme et al. were able to assign a central role to intrathecal immune activation, in particular monocyte activation in response to chemokine secretion, in triggering neuroinflammation and DCI (Mohme et al. 2020).

Further cellular components were identified that occur in the context of inflammation and can cause or aggravate vasoconstriction as well as infiltration of the intravascular system what might exacerbate the intravascular inflammation. These components include interleukins (IL-6, IL-1α, IL-1β, IL-8), TNF-α, LFA-1, leukotrienes, arachidonic acid, vWF, matrix metalloproteases (MMP-9) and VEGF (Schneider et al. 2018).

1.9. Cortical spreading depolarization

Another important influencing factor in the formation and effect of cerebral vasospasm is the CSD. It is characterized by a continuous cortical spreading depolarization of astrocytes and glial cells in the cortex. The end result is a change in the membrane potential of individual cell assemblies. In addition, interruption of synaptic transmission of stimuli may occur as part of CSD (Ayata and Lauritzen 2015). First demonstrated in 1944 using an animal model in epilepsy research, CSD is now known to influence the development of neurological diseases such as migraine, epilepsy, and in aneurysmal SAH (Sugimoto and Chung 2020).

The CSD has a propagation speed of only a few millimeters per minute. This results in a centrifugal propagation pattern in the gray matter. In the electroencephalogram (EEG), the CSD can be measured in the form of evoked and spontaneous EEG activities (Fujita et al. 2016).

The pathomechanism of CSD can be illustrated by the example of physiological stimulus conduction in healthy individuals (Wainsztein and Rodríguez 2018). Dendritic and somatic stimulus transmission is calcium-dependent and based on the inflationary occurrence of L-type calcium channels. The normal conduction of a cell

first requires the presence of a resting potential. The resting membrane potential (RP) is based on the principle of Brownian molecular motion (Daddi-Moussa-Ider and Gekle 2018).

Furthermore, to maintain this steady state of the RP, the cell requires certain ionic fluxes. These are potassium and sodium, which establish a concentration gradient through the activity of sodium-potassium ATPase. Here, the intracellular potassium concentration predominates over the extracellular one. Depending on the cell type, the cell membrane charge varies, ranging from -70mV to -90mV (Schmidt and Knösche 2019). An incoming action potential leads to depolarization of the cell membrane of the astrocytes and via an increase and ultimately the exceeding of the threshold potential. The consequence is an ion shift and the triggering of the action potential and stimulus conduction (Schmidt and Knösche 2019, Deemyad et al. 2018).

During CSD, depolarization results in overloading of the extracellular potassium clearance mechanism and a shift in threshold (Ayata and Lauritzen 2015). Triggered by the opening of non-selective cation channels, membrane resistance is reduced, resulting in an intra-extracellular ionic shift along the transmembrane concentration gradient (Wainsztein and Rodríguez 2018). In this regard, recent studies show an L-type calcium channel blocking property of the calcium channel blocker nimodipine, which may have a regulatory effect on CSD (Carlson et al. 2020).

A massive potassium efflux, with the assistance of sodium, chloride and calcium, leads to a widespread redistribution of water and ions and subsequent swelling of the

cell. The underlying pathophysiological mechanism of CSD is thus the increase in basal potassium concentration (Cenk and Lauritzen 2015).

A number of endogenous mechanisms, such as sodium-potassium ATPase, limit this effect in healthy individuals and ensure a prompt restoration of homeostasis under massive energy consumption (Wainsztein and Rodríguez 2018). It is precisely these repair mechanisms that can fail in a patient with aneurysmal SAH. As part of the acute bleeding event, there may be a reduction in ATP, an important fuel of sodium-potassium ATPase (Rajendran et al. 2016).

This process, in conjunction with reduced pumping power, leads to a long-term increase in intracellular calcium concentration in neurons and astrocytes and potentially to cell death. In this regard, the calcium channel blocker nimodipine was also able to reduce the intracellular calcium concentration in animal models and attenuate its neurotoxic effect (McLeod et al. 1998).

Dreier et al. recently found in animal experiments that CSD correlates electrophysiologically with the occurrence of neuronal cell swelling in the gray matter. The experimental data provide a perspective on the long-term use of measuring CSD which may serve as a real-time mechanistic biomarker to detect possible parenchymal damage after aneurysmal SAH and increased risk of poor neurological outcome (Dreier et al. 2022).

2. Methods

This section on `Methods´ is described in our already published article `*Safety and Clinical Effects of Switching from Intravenous to Oral Nimodipine Administration in Aneurysmal Subarachnoid Hemorrhage´* (Göttsche et al. 2021) and hence it will be referred to it.

2.1. Study population

This retrospective single center study included patients admitted to the University Medical Center Hamburg-Eppendorf with aneurysmal SAH between 01/14 – 04/18 and initial i.v. nimodipine therapy over at least 48h, which was subsequently switched to oral administration. Basic clinical characteristics of our study population were collected including clinical parameters and aneurysmal SAH-relevant events on ICU at admission and during hospitalization as well as medical history. Demographic information, aneurysm location, information on antiplatelet aggregation medication, pre-existing conditions and distinct clinical evaluation scores (GCS, Hunt&Hess grading system, WFNS grading system, Fisher Score) were included in this data collection. The drug doses could be extracted from the intensive care unit's electronic documentation system (Integrated Care Manager, Dräger Medical Deutschland GmbH, Lübeck, Germany) and the clinical documentation System SOARIAN (Cerner Soarian Clinicals, Version 4.3.200) (Göttsche et al. 2021).

Our study was conducted in accordance with the Declaration of Helsinki, local and institutional laws and was reported to the local ethical committee (No. WF-039/20). Written informed consent was waived for this kind of study (Göttsche et al. 2021).

2.2. Treatment protocol

Patients were treated according to common guidelines and as previously described (Connolly et al. 2012, AWMF). After initiation of i.v. nimodipine (Nimotop S, Bayer Vital, Leverkusen, Germany) therapy directly after admission, this medication was continued for at least 8 days as an uninterrupted infusion of 2 mg/h. Depending on the clinical situation, including the level of analgosedation or already evident cerebral vasospasm or perfusion deficits, the switch to enteral administration was conducted. Enteral administration was 60 mg (two tablets) orally every 4 hours apart. Tablets were crushed and washed down a nasogastric tube with normal saline in patients unable to swallow (Abboud et al. 2015, Czorlich et al. 2017). If cerebral vasospasm, perfusion deficits, or neurological deficits were detected, i.a. lysis with nimodipine as rescue-therapy was performed (Göttsche et al. 2021).

2.3. Transcranial Doppler device

Beginning on the first day after admission, Transcranial Doppler sonography of the ACA as well as the MCA was performed daily via the transtemporal window. All measurements were performed with the same device (DWL Multi-Dop T Digital, Compumedics Germany GmbH, Singen, Germany) using a 2 MHz frequency ultrasound probe. To avoid examiner-dependent bias, the measurements were mainly carried out by the same trained medical technical assistant and the mean flow velocities were recorded. Cerebral vasospasm was suspected by TCD if the mean flow velocity in the ACA was above 120 s/m and in the ACM was above 140cm/s (Göttsche et al. 2021).

2.4. Definitions of cerebral vasospasm and delayed cerebral ischemia

As earlier defined according to Vergouwen et al., the occurrence of cerebral vasospasm and DCI during the overall course of the treatment was detected via TCD, CTA, CT-perfusion imaging (CTP) and DSA (Vergouwen et al. 2010). In some cases of partially sedated patient population, the determination of clinical worsening is difficult or not possible (Schmidt et al. 2008). Therefore, in case of Doppler sonographic suspicion of cerebral vasospasm, a confirmed narrowing of the vessels in the above-mentioned imaging was considered a cerebral vasospasm (Göttsche et al. 2021).

The following subgroups were defined depending on neurological parameters and TCD, to assess, whether there were differences within these groups, that would further increase significance: a) patients who had neither cerebral vasospasm nor infarctions, patients in whom either b) cerebral vasospasm or c) infarctions could be detected and d) patients in whom both were present (Göttsche et al. 2021).

2.5. Data analysis

Data was extracted from the clinical documentation systems as mentioned earlier. Medication was extracted as flowrate of a continuous application (nimodipine and norepinephrine) or as time of administration (nimodipine oral). Cumulative drug dosage over 24h was calculated to carry out possible correlations with measured TCD values (typically one per day) (Göttsche et al. 2021).

Qualitative variables are outlined as number and percentage, quantitative variables were described as mean and standard deviation (SD). To assess the timepoint of change against the cumulative dosage of drugs was used to indicate for an

overlapping dosage phase. Only timepoint of consecutive changes nimodipine i.v. to oral were assigned. Some patients had a longer overlapping time (max. 48h). These values are depicted separately and not applied for paired analysis. Some of the patients presented two phases of changes. In these cases the last change was considered. We performed a gathered analysis of values from ACA and MCA and also of all values combined to show that even when combining values no significant change was observed (Göttsche et al. 2021).

2.5.1. Statistical analysis

Statistical analysis of the data was performed by a univariate analysis using chi-squared tests, independent-samples Kruskal-Wallis tests or ANOVA tests depending on the scale of the measurements and equality of variances. We calculated the linear regression coefficient to examine correlations between the parameters. The level of statistical significance was set at $p<0.05$. The time since ICU admittance was tiled and we calculated the mean (points) and standard error of mean (error bars) to visualize the parameters from the digital patient record (Göttsche et al. 2021).

Data transformation, calculation and visualization was done in R (version 3.6.3 main packages: dplyr, tidyverse, stringr, ggplot2, ggpubr). For final composition of figures we used Adobe Illustrator (Adobe Inc., San José, USA; Version 24.3) (Göttsche et al. 2021).

3. Results

This section on `Results´ is also described in our already published article `*Safety and Clinical Effects of Switching from Intravenous to Oral Nimodipine Administration in Aneurysmal Subarachnoid Hemorrhage´* (Göttsche et al. 2021) and hence it will be referred to it.

3.1. Patient characteristics

We analyzed 133 patients after aneurysmal SAH initially receiving nimodipine i.v. which was switched to oral administration during the mean course of 11.7 ± 5.78 days. 87 female and 46 male patients with a mean of 56 ± 13.7 years of age were included in this study. Aneurysms of the anterior circulatory system were found to be the most common cause of SAH in those patients (70.7%) (Göttsche et al. 2021).

In 30% of the cases, cerebral vasospasm had been detected via CTA, CTP and DSA imaging. In addition, 20.3% of the patients with cerebral vasospasm had an infarction on imaging. An infarction could be documented without prior evidence of cerebral vasospasm in 14.3% of the cases. A total of 42.9% of the patients were classified as an uncomplicated course of aneurysmal SAH, since neither cerebral vasospasm nor infarctions occurred (Göttsche et al. 2021).

Patient cohorts were then divided and defined according to these findings further on: Patients who had an uncomplicated course (UC) represented the major group with 57 patients. In 30 cases (22.6%) cerebral vasospasm (CVS) occurred, 19 patients (14.3%) suffered from cerebral infarction (CI) and cerebral vasospasm plus cerebral infarction (CVS+CI) occurred in 27 cases (20.3%), Table 4 (Göttsche et al. 2021).

Table 4: Patient characteristics

	UC	CVS	CI	CVS+CI
Number of patients (%)	57 (42.9)	30 (22.6)	19 (14.3)	27 (20.3)
Sex – no. (%)				
male	22 (38.6)	7 (23.3)	9 (47.4)	8 (29.6)
female.	35 (61.4)	23 (76.7)	10 (52.6)	19 (70.4)
Age – mean (sd)	56.5 (14)	54.1 (13.4)	59.2 (13.4)	55.1 (13.9)
Localization of aneurysm (Circulation) – no. (%)				
anterior	39 (68.4)	20 (66.7)	10 (52.6)	25 (92.6)
posterior.	18 (31.6)	10 (33.3)	9 (47.4)	2 (7.4)
Hunt & Hess grade – no. (%)				
1	12 (21.1)	4 (13.3)	5 (26.3)	5 (18.5)
2	18 (31.6)	11 (36.7)	4 (21.1)	6 (22.2)
3	9 (15.8)	8 (26.7)	4 (21.1)	6 (22.2)
4	6 (10.5)	5 (16.7)	1 (5.3)	3 (11.1)
5	12 (21.1)	2 (6.7)	5 (26.3)	7 (25.9)
Fisher grade – median (IQR)	4.0 (±1.0)	4.0 (±1.0)	4.0 (±0.5)	4.0 (±0.5)
WFNS grade – median (IQR)	1.5 (±3.2)	2.0 (±2.8)	1.0 (±4.0)	2.5 (±3.8)
initial GCS – median (IQR)	15.0 (±9.0)	14.0 (±3.5)	14.0 (±6.0)	13.0 (±8.5)
Pre-existing conditions – no. (%)				
arterial hypertension	22 (38.6)	13 (43.3)	9 (47.4)	10 (37.0)
alcohol abuse	5 (8.8)	1 (3,3)	0	0
chronic headache	3 (5.3)	4 (13.3)	2 (10.5)	3 (11.1)
diabetes mellitus	2 (3.5)	0	0	1 (3.7)
cardiovascular desease	8 (14.0	3 (10.0)	3 (15.8)	4 (14.8)
smoking	13 (22.8)	6 (20.0)	5 (26.3).	6 (22.2)
platelet aggregation inhibitors in premedication – no. (%)	32 (56.1)	11 (36.7)	12 (44.4)	16 (84.2)
stay on ICU (days) – mean (sd)				
outcome – no. (%)	17.5 (10.8)	19.2 (7.8)	24.3 (12.3)	18.7 (9.2)
deceased	9 (15.8)	3 (10)	6 (22.2)	3 (15.8)
survived	48 (84.2)	27 (90)	21 (77.8)	16 (84.2)

GCS = Glasgow Coma Scale; ICU = intensive care unit; IQR = interquartile range;
sd = standard deviation; WFNS = World Federation of Neurosurgical Societies;
UC= uncomplicated course, CVS= cerebral vasospasm; CI= cerebral infarction

3.2. Flow velocities values pre and post nimodipine switch

During the switching period the flow velocities on TCD were examined more closely. The mean flow velocity 24 hours before switching to oral administration was 83.82 cm/sec in the MCA and 64.83 cm/sec in the ACA. Mean flow velocities on TCD on the first day after the switch were 81.82 cm/sec and 64.57 cm/sec, respectively. This analysis was furthermore carried out depending on the occurrence of complications and examined for the subgroups mentioned above (Göttsche et al. 2021).

Prior to the switch, the mean flow velocities of the MCA were 74.87 cm/sec in the group without complications, 62.36 cm/sec in the cerebral infarction group, 98.88 cm/sec among patients with cerebral vasospasm and 93.80 cm/sec in the cerebral vasospasm plus cerebral infarction subgroup. Mean values of 58.68 cm/sec in the patient group with an uncomplicated course, 60.40 cm/sec in the group showing cerebral infarction, 72.89 cm/sec in the patients with cerebral vasospasm, and 66.56 cm/sec in the group of patients indicating cerebral vasospasm plus cerebral cerebral infarction were measured for the ACA before the switch (Göttsche et al. 2021).

There were no significant increases in mean flow velocities on TCD on the first day after switching the route of i.v. application to oral application in either subgroup of patients except for MCA in the cerebral infarction group (Table 5). Mean flow velocities of the MCA in the group with uncomplicated course were 72.87 cm/sec and 90.45 cm/sec in the group cerebral vasospasm plus cerebral infarction. With respect to the ACA, mean values of 62.24 cm/sec in the patients with uncomplicated course and 67.50 cm/sec in the group of cerebral vasospasm plus cerebral infarction were noticed (Göttsche et al. 2021).

Table 5: Flow velocities values pre and post nimodipine switch

subgroup	Pre (in cm/sec) mean (sd)	Post (in cm/sec) mean (sd)	*p*-value
ACA			
overall population	64.83 ± 27.91	64.57 ± 22.75	0.93
UC	58.68 ± 22.26	62.24 ± 24.11	0.38
CI	60.40 ± 29.88	63.80 ± 19.14	0.45
CVS	72.89 ± 34.43	66.00 ± 22.79	0.30
CVS+CI	66.56 ± 23.12	67.50 ± 23.31	0.90
MCA			
overall population	83.82 ± 37.54	81.82 ± 30.53	0.48
UC	74.87 ± 31.73	72.87 ± 30.26	0.63
CI	62.36 ± 22.43	71.78 ± 22.26	<0.01
CVS	98.88 ± 46.19	92.97 ± 29.82	0.34
CVS+CI	93.80 ± 30.05	90.45 ± 30.36	0.67

ACA = anterior cerebral artery; CVS = cerebral vasospasm; CI = cerebral infarction; MCA = middle cerebral artery; Pre = one day before nimodipine iv switch to oral administration, Post = first day of oral nimodipine administration, sd = standard deviation; UC = uncomplicated course

3.3. Analysis of Transcranial Doppler sonography-values during the switch of the route of administration

We performed an analysis of the last day of i.v. administration of nimodipine versus the first day of the full oral dose. No significant changes in the flow velocities of the middle and anterior cerebral arteries could be measured (Figure 7A, 7B) (Göttsche et al. 2021).

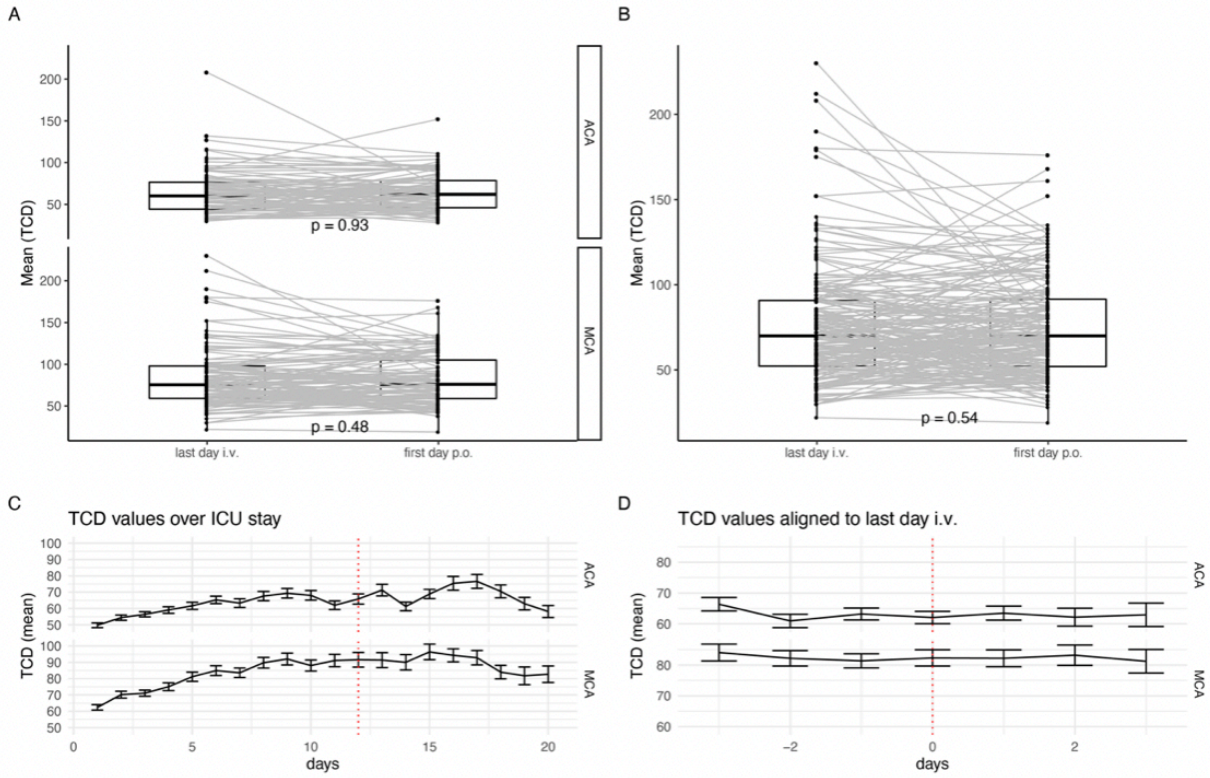

Figure 7: Analysis of TCD-values during the switch of the route of administration

A: The TCD values are measured longitudinal in patients. Only patients with consecutive values before and after switching the route of administration of nimodipine are depicted. Values for A. cerebri anterior (upper) and A. cerebri media (lower) are depicted separately.
B: All TCD values independent of their circulation are depicted. The lower and upper hinges of the boxplots correspond to the first and third quartile of all values. The whiskers represent the 1.5 interquartile range (IQR). Dots show each value and grey lines connect individual patients' measurements. Statistical analysis was performed with paired t-test.
C: Mean TCD values are shown over the first 20 days of ICU stay for A. cerebri anterior (upper) and A. cerebri media (lower). Error bars represent the standard deviation.
D: Mean TCD values aligned to the individual switch of the route of administration. Whiskers represent. Error bars represent the standard deviation.

The mean TCD values collected in the course of time during the intensive care stay and especially during the switch are shown in Figure 7C and 7D (Göttsche et al. 2021).

The above-mentioned subdivision into subgroups was applied for a more detailed description of the heterogeneous collective; in addition, the values for ACA and MCA

are listed separately (Figure 8). There were no significant increases detected after switching the type of administration (Göttsche et al. 2021).

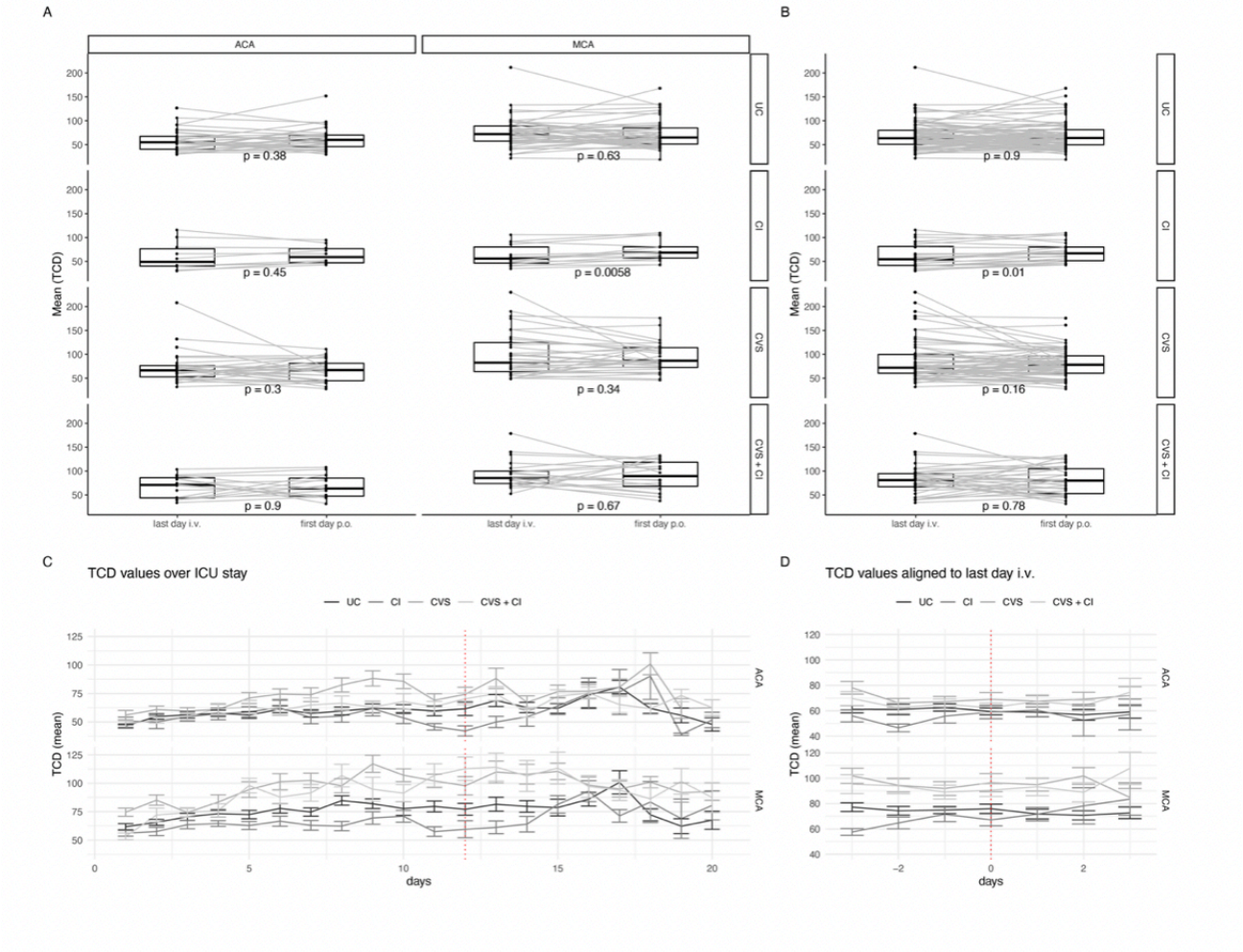

Figure 8: Analysis of TCD-values of subgroups during the switch of the route of administration

The TCD values are measured longitudinal in all patients during the ICU stay. Grouping is done according to radiological findings: Uncomplicated course (UC), cerebral infarction (CI), cerebral vasospasm (CVS) and cerebral vasospasm plus cerebral infarctions (CVS + CI).

A: Only patients with consecutive values before and after switching the route of administration of nimodipine are depicted. Values for A. cerebri anterior (left) and A. cerebri media (right) are depicted separately.

B: All TCD values independent of their circulation are depicted. The lower and upper hinges of the boxplots correspond to the first and third quartile of all values. The whiskers represent the 1.5 interquartile range (IQR). Dots show each value and grey lines connect individual patients' measurements. Statistical analysis was performed with paired t-test.

C: Mean TCD values are shown over the first 20 days of ICU stay for A. cerebri anterior (upper) and A. cerebri media (lower). Error bars represent the standard deviation.

D: Mean TCD values aligned to the individual switch of the route of administration. Whiskers represent. Error bars represent the standard deviation.

3.4. Temporal resolution of complications in subgroups in relation to the timing of the switch

There could not be observed a significant increase in flow velocities during the switch or on the day after the switch compared to the day before the switch (last day i.v.) (Figure 9A, 9B) (Göttsche et al. 2021).

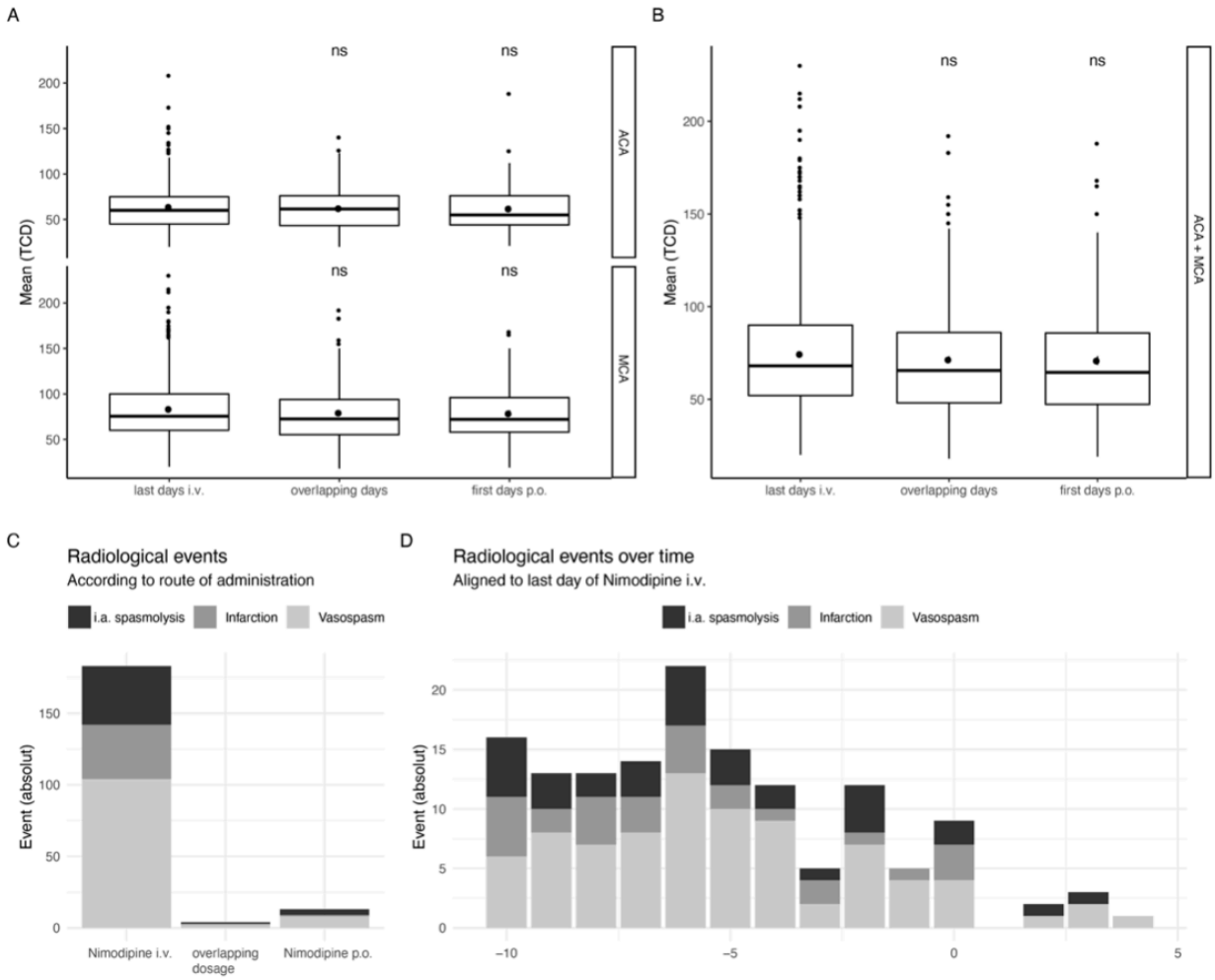

Figure 9: Temporal resolution of complications in subgroups in relation to the timing of the switch

Taking all measured TCD values in account of all patients included in the study not only longitudinal but all values were considered. The TCD values on the last two days of nimodipine i.v. and the first two days of oral administration only were depicted, together with overlapping dosages.

A: Values for A. cerebri anterior (upper) and A. cerebri media (lower) are depicted separately.
B: All TCD values independent of their circulation are depicted. The lower and upper hinges of the boxplots correspond to the first and third quartile of all values. The whiskers represent the 1.5 interquartile range (IQR). Statistical analysis was performed with unpaired t-test compared to the last day of i.v. administration.
C: Absolute amount of the radiological events are show according to the administered drug.
D: Radiological events over all the ICU stay (absolute numbers).

A significant increase in flow velocities during the switch or on the days after the switch compared to the days before the switch (last day i.v.) was shown in none of the groups with complications (cerebral vasospasm, cerebral infection and cerebral vasospasm plus cerebral infarction) (Figure 10A, 10B) (Göttsche et al. 2021).

In an unpaired analysis, the combination of flow velocities of ACA and MCA revealed significantly lower flow velocities among the uncomplicated courses on the first day after the switch (Figure 9B). No additionally significant changes on TCD during the switching period were found (Figure 9A, 9B) (Göttsche et al. 2021).

In a next step, the time course of the complications that occurred in relation to the timing of oralization was examined. We found no accumulation of complications like cerebral vasospasm or cerebral infarction after or during the switch of the route of administration (Figure 9C, 9D and 10C, 10D): in the cerebral vasospasm plus cerebral infarction group 93 events occurred during the intravenous administration period. Of these events, 18 were intraarterial spasmolysis with locally administered nimodipine. After the switch, 8 events occurred in the same, of which 3 were intraarterial spasmolysis with locally administered nimodipine (Göttsche et al. 2021).

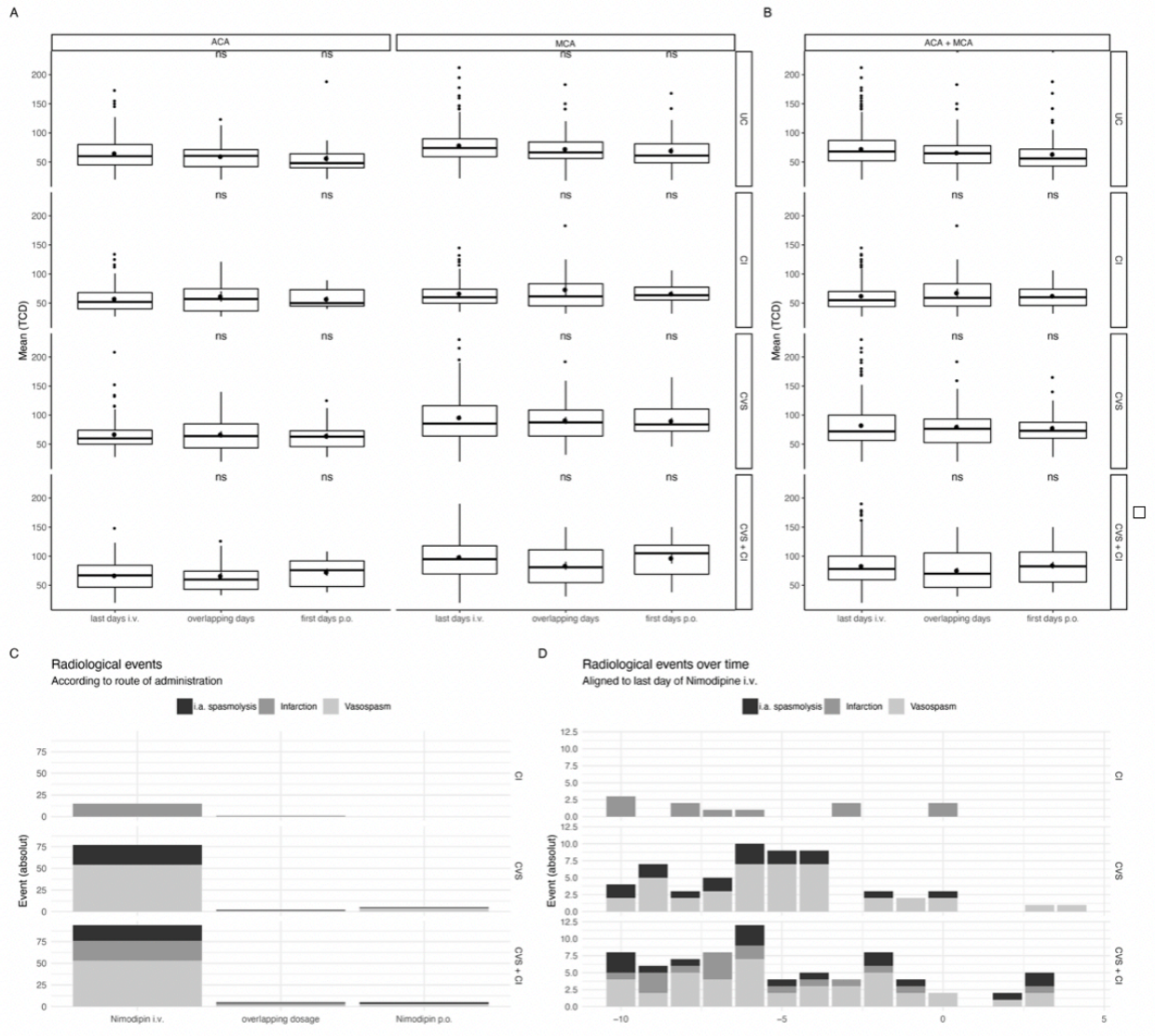

Figure 10: Temporal resolution of complications in subgroups in relation to the timing of the switch

Taking all measured TCD values in account of all patients included in the study not only longitudinal but all values were considered. The TCD values on the last two days of nimodipine i.v. and the first two days of oral administration only were depicted, together with overlapping dosages. Grouping is done according to radiological findings: Uncomplicated course (UC), cerebral infarction (CI), cerebral vasospasm (CVS) and cerebral vasospasm and cerebral infarctions (CVS + CI).

A: Values for A. cerebri anterior (upper) and A. cerebri media (lower) are depicted separately.
B: All TCD values independent of their circulation are depicted. The lower and upper hinges of the boxplots correspond to the first and third quartile of all values. The whiskers represent the 1.5 interquartile range (IQR). Statistical analysis was performed with unpaired t-test compared to the last day of i.v. administration.
C: Absolute amount of the radiological events are show according to the administered drug.
D: Radiological events over all the ICU stay (absolute numbers).

Cerebral infarction was mainly detected in the first ten days of ICU stay, which is in line with detection of cerebral vasospasm. In 93 of a total of 124 cerebral vasospasm occurred within the first ten days. Furthermore, 37 of a total of 46 cerebral infarction occurred and 35 of a total of 50 i.a. spasmolysis were performed within the first ten days (Göttsche et al. 2021).

3.5. Norepinephrine dose around nimodipine switch

The mean catecholamine dose decreased significantly in all groups after the switch. Before the switch, the norepinephrine dose ranged from 7 to 13 mg/day (depending on the group, Table 6) compared to 4 - 8 mg/day after the switch. The systemic mean arterial pressure remained constant during the switch (Göttsche et al. 2021).

Table 6: Norepinephrine dose around nimodipine switch [mg/day]

	Pre mean (sd).	Post mean (sd)	*p*-value
UC	9 (7)	4 (5)	<0.0001
CI	7 (7)	4 (3)	0.03
CVS+CI	13 (10)	8 (6)	<0.0001

To further investigate the changes in nimodipine dosage and their impact on the underlying changes in flow rates, correlation analyses were performed (Figure 11) (Göttsche et al. 2021).

3.6. Correlation of Transcranial Doppler sonography-values to oral and i.v. nimodipine

Oral nimodipine shows a negative correlation coefficient in the uncomplicated course group and cerebral vasospasm group while i.v. nimodipine shows no relevant correlation (Göttsche et al. 2021).

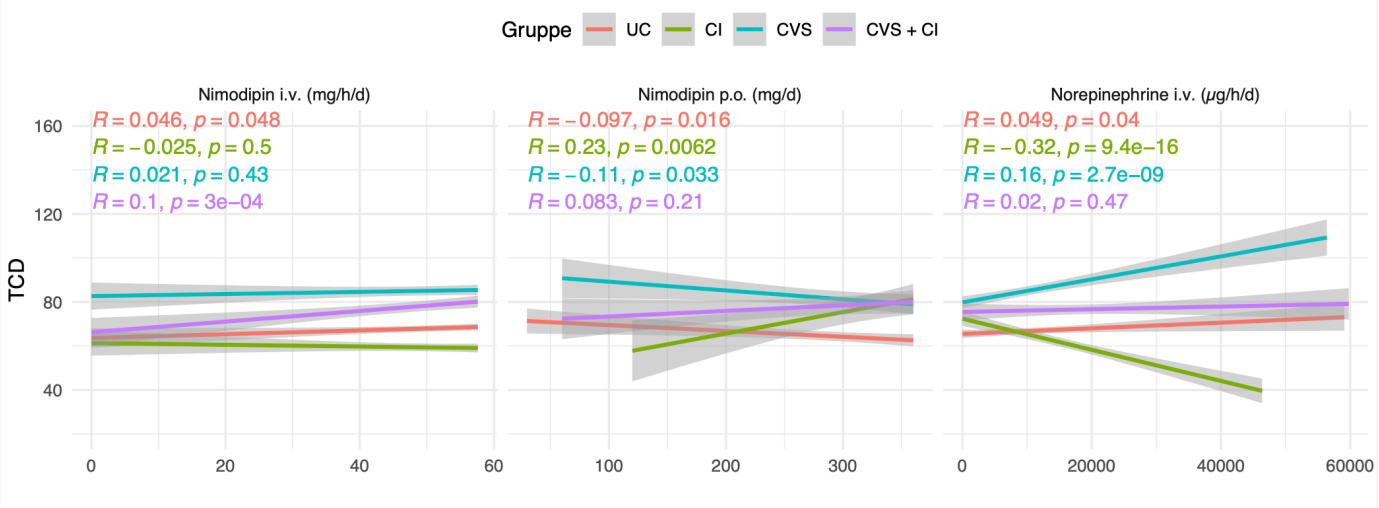

Figure 11: Correlation of Transcranial Doppler Sonography to oral and i.v. nimodipine

Groups: Red line – uncomplicated course (UC); green line cerebral infarction (CI), blue line cerebral vasospasm (CVS), and purple line cerebral vasospasm plus infarction (CVS+CI). To unveil dosage effects correlation analysis were done. All TCD values are depicted and correlated to the nimodipine i.v., oral and norepinephrine cumulative dosage over 24h. Linear regression line with the according standard error are depicted for the defined groups. Pearson correlation coefficient and the according p-value are shown in the upper left of the plots.

4. Discussion

In order to interpret the results of the present study and to place them in the context of current therapy, the mode of action and previous clinical use of the calcium antagonist nimodipine will be explained at first.

4.1. Therapeutic significance of the calcium channel blocker nimodipine

4.1.1. The working principle of nimodipine

In the last three decades, new approaches to the treatment of cerebral vasospasm have been increasingly found, especially in the field of experimental pharmacology. The calcium canal blocker nimodipine from the group of dihydropyridines is so far the only drug substance which has been shown to improve the outcome of patients after aneurysmal SAH and has been able to establish itself as a primary pharmaceutical in the treatment of aneurysmal SAH (Petruck et al. 1988).

The mechanism of action of calcium channel blockers has already been well understood long before and these substances are the established gold standard in the treatment of patients with hypertension (Elliott and Ram 2011). The working principle is the inhibition of voltage-dependent L-type Ca2+ channels on cardiac and vascular smooth muscle cells. The consequence is a reduced Ca2+ influx into the cell, leading to a negative inotropic effect with vasodilation and decreased afterload at the cardiac level (Yalamanchili et al. 1998). The processes at the cellular level are shown schematically in Figure 12. Of the group of these substances, the active ingredient nimodipine (Nimotop®, Bayer AG) is of particular interest.

The substance is blood-brain barrier mobile (Scriabine and Kerckhoff 1988). Originally developed for the treatment of hypertension, nimodipine is currently

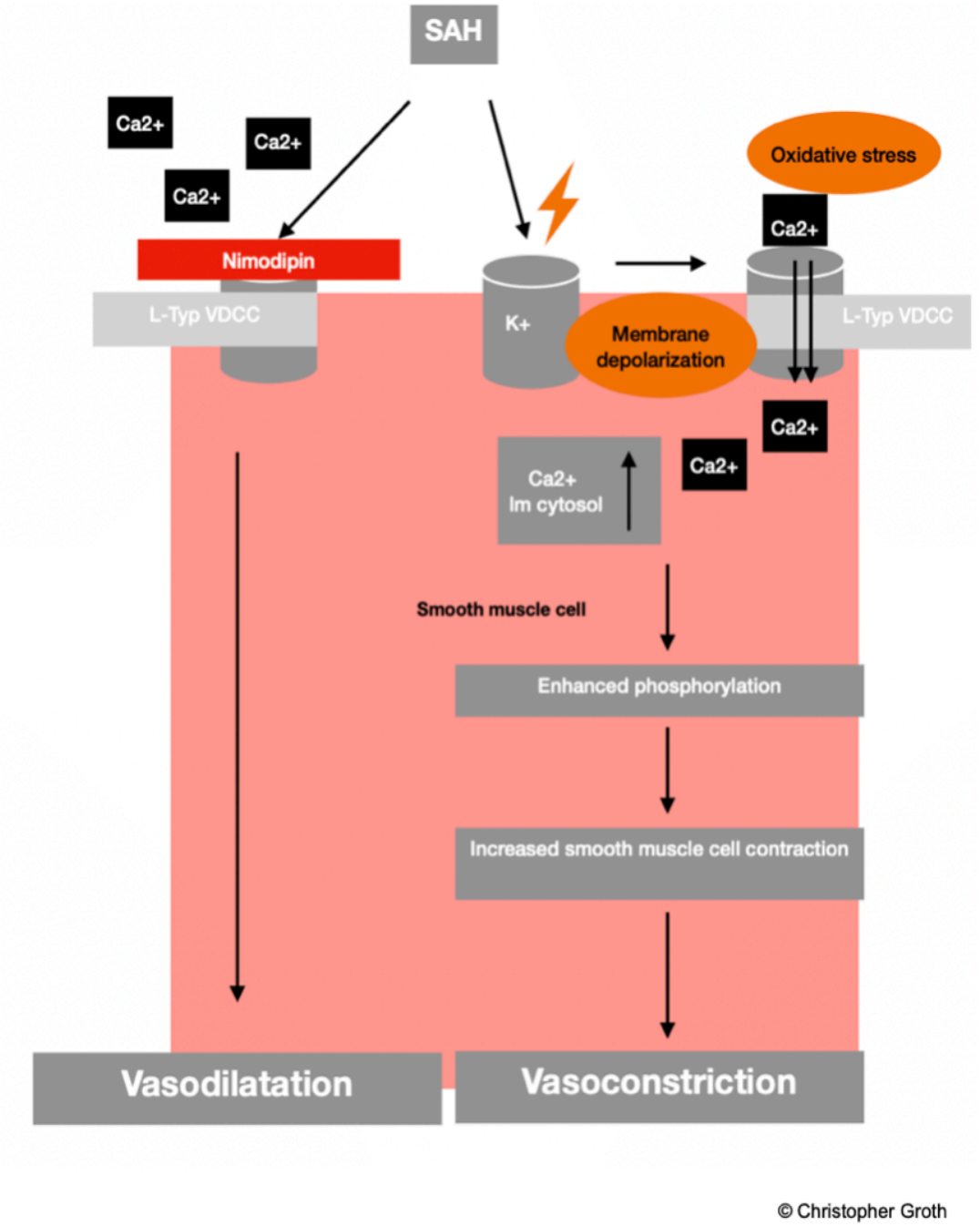

Figure 12: Schematic representation of the mode of action of nimodipine in SAH

approved in the U.S. only for aneurysmal SAH (Hajizadeh et al. 2019). Evidence of the beneficial vascular effect of nimodipine on cerebral blood flow (CBF) existed as

early as 1989, with one study showing significantly higher CBF in the nimodipine cohort compared with placebo cohort. A significant benefit for patient outcome could not be shown at that time (Forsman et al. 1989). As mentioned above, the calcium channel blocker nimodipine can reduce intracellular calcium concentrations (McLeod et al. 1998).

The molecular mechanism of action of nimodipine results in a prompt correction of neurovascular conduction, leading to an immediate effect after CSD toward restoration of homeostasis in the parenchyma (Carlson et al. 2020).

The extent to which nimodipine modulates stimulus conduction in the context of CSD remains to be determined. Nimodipine has been shown to reduce the initiation of CSD (Carlson et al. 2020). Thus, it may be possible to influence neuronal damage after aneurysmal SAH by re-activating neurovascular mechanisms, thus attributing a novel neuroprotective role to the drug nimodipine. Whether this applies only to a specific patient population remains to be tested in the future.

4.1.2. Pharmacokinetics of nimodipine

Important parameters for describing the pharmacokinetics of a drug are its distribution, absorption rate, metabolism, and excretion (Starkey and Sammons et al. 2015).

The pharmacokinetics of nimodipine have been well understood since the 1980s and have been demonstrated in numerous studies (Möller 1999). Nimodipine belongs to the calcium antagonists of the dihydropyridine class. Plasma concentrations reach their maximum within 30 – 60 minutes. The relatively low bioavailability is due to the

metabolic factor of the first-pass effect, similar to many drugs (Möller 1999). The metabolization of nimodipine is dihydropyridine-specific, with a minor exception in the form of additional demethylation. According to the structure, dehydrogenation of the dehydropyridine ring is the first step. Demethylation is followed by dehydrogenation, at the end of which is the hydroxylation of the methyl group (Möller 1999).

The biological half-life period of nimodipine is 1.7 – 2 hours when administered orally, with peak levels reached after one hour. When administered orally, nimodipine is almost completely gastrointestinally absorbed and distributed in healthy subjects. A process that is delayed in 60% of patients with aneurysmal SAH according to Nguyen et al (Nguyen et al. 2007).

It is believed that in patients in the intensive care setting, the clouded-conscious state and malabsorption in the gastrointestinal tract may have an impact on the pharmacokinetics of nimodipine (Nguyen et al. 2007).

4.2. Studies on dose optimization - management of side effects in the clinical setting

The standard dosage for drug treatment of cerebral vasospasm is nimodipine 60 mg every 4 hours per os for 3 weeks. The guideline recommends administration of oral nimodipine in patients with aneurysmal SAH (Van Gijn et al. 2007, Dorhout Mees et al. 2007, Connolly et al. 2012, AWMF). Intravenous nimodipine use is limited in dosage due to its blood pressure-lowering effect. On average, this drug-induced hypotension occurs in ≤56% of patients (Sandow et al. 2016).

Nevertheless, it is common practice in neurological/neurosurgical ICUs to administer nimodipine intravenously, at least in the early phase of treatment. Based on current knowledge, nimodipine is the only effective primary prevention of DCI after aneurysmal SAH (Dorhout Mees et al. 2007).

In the treatment of aneurysmal SAH with nimodipine, associated arterial hypotension is a particularly influential side effect. The guideline recommends a mean arterial pressure with target values between 60 - 90 mmHg in the setting of aneurysmal SAH. A widely used form of therapy to combat cerebral vasospasm was the so-called triple-H therapy. It insisted on the parameters of hypertension, hypervolemia and hemodilution. However, its utility has been increasingly questioned due to clinical morbidity especially due to the high catecholamine dosages (Lee et al. 2006). Against this background, the requirement for deliberately induced hypertension when neurological status worsens (Connolly et al. 2012, Steiner et al. 2013) needs to be weighed.

Due to the hypotensive effect of nimodipine, this is initially in contrast to the formulated therapeutic principles. However, Sandow et al. were able to demonstrate in 2016 that nimodipine-induced hypotension can be compensated with adjusted catecholamine administration and does not worsen patient outcome (Sandow et al. 2016).

Induced hypertension to avoid DCI in aneurysmal SAH was topic of the randomized controlled HIMALAIA trail, which was soon ended due to serious adverse events and a lack of effect (Gathier et al. 2018). A rational balance between a constant MAP and nimodipine dosing in patients after aneurysmal SAH should be further pursued.

Efforts should be made to define a maximum catecholamine dosage and an individualized and optimized MAP below which nimodipine dose reduction or discontinuation should occur in the clinical setting. In this regard, reliable data must be generated in the coming years.

4.3. Studies on optimized administration of nimodipine - literature overview

In 2015, Abboud et al. reported the superiority of the i.v. administration of nimodipine in patients with aneurysmal SAH in terms of serum concentration of the drug. They showed a dependence between the clinical condition of the patient, the route of administration, and the serum concentration. In this regard, intravenous nimodipine proved superior to enteral administration, especially in patients with dysphagia (Abboud et al. 2015). The correlation of possibly lower nimodipine serum concentrations with increased occurrence of cerebral vasospasm had not been investigated in this context.

In 2016, the research group around Sandow et al. addressed the question of the clinical significance and effect of nimodipine dose reduction in patients with aneurysmal SAH. This study showed that patients, who had nimodipine reduced or stopped were more likely to be diagnosed with DCI. The data reaching statistical significance in patients with Hunt and Hess Grade “I-III” ($p = 0.037$) (Sandow et al. 2016). In addition, the study found that nimodipine dose reduction was not associated with angiographic cerebral vasospasm, but was associated with poor outcome depending on the patient's age and Hunt and Hess grade (Sandow et al. 2016).

Frequently, nimodipine reduction followed a reduced mean arterial pressure (MAP), a current phenomenon in clinical routine. Additionally, the research group included the increased vasopressin administration in the study and recommended close monitoring (Sandow et al. 2016). A clear recommendation regarding the optimal safe conditions for nimodipine reduction could not be made.

In 2017, the intriguing question of optimal dosing with apparently limited applicability led to the idea of a randomized, open-label dose-escalation study with intraventricular nimodipine application, where the drug was here coated with pH-sensitive nanoparticles to selectively target specific tissue areas and circumvent systemic side effects. The dose range was 100mg to 1200mg. The aim was to investigate pharmacokinetics and any improvement in outcome (Hänggi et al. 2017). The maximum tolerable dose was 800mg. A significant benefit of intraventricular nimodipine application in terms of complications such as DCI, angiographic cerebral vasospasm, cortical spreading ischemia, microthromboembolism and loss of autoregulation could not be demonstrated (Hänggi et al. 2017).

In conclusion, the current recommendation is for oral administration of nimodipine as cerebral vasospasm prophylaxis after aneurysmal SAH (Dorhout Mees et al. 2007). However, there is evidence that this route of administration has lower bioavailability compared with intravenous administration, especially in patients with analgesia (AWMF guideline), so that in practice oral and intravenous administration are used depending on clinical conditions and local treatment regimens.

4.4. Findings from the study on safety and clinical effects of switching from i.v. to oral nimodipine administration in aneurysmal subarachnoid hemorrhage

This subtopic of `Discussion´ is already described in our published article `*Safety and Clinical Effects of Switching from Intravenous to Oral Nimodipine Administration in Aneurysmal Subarachnoid Hemorrhage´* (Göttsche et al. 2021) and hence it will be referred to it.

Basically, both intravenous and oral administration of nimodipine appear to be justified and, in addition to intra-arterial rescue therapy, play a relevant part in everyday clinical practice (Kieninger et al. 2018). Past studies showed no significant difference in terms of plasma concentration or efficacy achieved when comparing oral with intravenous administration (Kronvall et al. 2009, Albania et al. 2017, Kieninger et al. 2019). Despite the known data with regard to bioavailability, to the best of our knowledge, studies investigating a switch from intravenous to oral nimodipine administration are entirely missing in the literature (Connolly et al. 2012, Abboud et al. 2015, Göttsche et al. 2021).

The mentioned lower oral bioavailability of nimodipine, especially in analgosedated patients, as well as the frequent blood pressure-related omission of oral administration make i.v. administration of the drug a common and valid alternative (Abboud et al. 2015, Sandow et al. 2016, Isse et al. 2020, Göttsche et al. 2021). Sandow et al. demonstrate low blood pressure to be often leading to dose reductions or skipping of oral doses, which may be associated with unfavorable outcome (Sandow et al. 2016). When administered intravenously, there is a reduced risk of lower bioavailability in sedated patients. Intravenous nimodipine therapy is therefore

often used initially in the intensive care therapy of aneurysmal SAH patients followed by a switch to oral administration in the later phase (Göttsche et al. 2021).

In relation to this clinically relevant topic, we were able to show that almost no significant change in flow velocities or incidence of negative clinical events occurred after the switch. Although flow velocities in the cerebral infarction group increase significantly on the first day after the switch, shown in Table 2, a closer examination does not show any clustering of relevant events (Figure 9D) (Göttsche et al. 2021).

Because the patient collective is heterogeneous and includes patients with complications as well as uncomplicated courses, all parameters of the subgroups in which complications occurred followed systematically examination to raise the sensitivity of the analyses. Even though we explicitly looked into patients with complications and compared them with uncomplicated courses, no differences were found (Göttsche et al. 2021).

It has to be noted that the switch was conducted at a mean of 12 days after the patients admission to the ICU and thus at a time when the risk for cerebral vasospasm is still present but decreasing (Weir et al. 1978, Parsons and Wiener-Kronish 2007, Göttsche et al. 2021).

Although this work has some limitations such as its retrospective and single-center design, we were nevertheless able to show the effects of a change in the application method on flow rates and the occurrence of complications in a well-documented, representative cohort (Göttsche et al. 2021).

To strengthen the value of our findings, it would be desirable to determine the serum concentrations of nimodipine measured before, during and after the nimodipine switch. Since measurement of serum nimodipine concentration is not a standard procedure in our facility, data are not available for this retrospective analysis, but should be included in future prospective studies.

Further prospective studies will have to investigate the potential benefit of initial intravenous nimodipine therapy. Our data and the considerations for intravenous administration can be relevant for studies comparing standard nimodipine therapy with an investigational drug as the NEWTON trial (Hänggi et al. 2017, Göttsche et al. 2021).

4.5. Alternate therapeutical approaches in terms of cerebral vasospasm - a future prospect

In 2004, the potent endogenous vasoconstrictor endothelin has been implicated in the pathogenesis of cerebral vasospasm. In experimental models of aneurysmal SAH, endothelin receptor antagonists had been able to reduce cerebral vasospasm (Zimmermann and Seifert 2004).

Recent clinical trials have demonstrated marked prevention of cerebral vasospasm with the endothelin receptor antagonist clazosentan, yet patient outcome was not improved. However, the CONSCIOUS-1 and CONSCIOUS-2 phase 2 and 3 trials investigated the use of clazosentan to overcome neurological ischemia and infarction occurring after aneurysmal SAH in a randomized, double-blinded, placebo-controlled clinical trial using clazosentan, revealed successful reduction of the relative risk of angiographic cerebral vasospasm by 65%. However, the CONSCIOUS-1 trial

revealed that clazosentan could not improve mortality or clinical outcome (Macdonald et al. 2008, Leng et al. 2011, Macdonald et al. 2011).

Another vasodilatator studied in the context of aneurysmal SAH is the potent RhoA/Rho kinase (ROCK) inhibitor fasudil. Via inhibition of free intracellular calcium, as well as inhibition of protein kinases A, G and C, the drug has been repeatedly shown to have beneficial effects on development of cerebral vasospasm, DCI as well as on the patients outcome. Even in the comparison with nimodipine, fasudil showed improved outcome. A large multicenter study is yet to be accomplished (Budohoski et al. 2014).

Other studies have focused on microcirculatory disturbance like microthrombosis and arteriolar constriction as a factor relevant for CI after aneurysmal SAH, whose role will further be discussed in the future (Leng et al. 2011).

Concerning blood pressure management in early stages of aneurysmal SAH, the optimal approach is still unclear. Observational studies suggest blood pressure optimization as a neuroprotective strategy after demonstrating worse outcomes in patients with increased hemodynamic variability (Silverman et al. 2019).

In my opinion, the increasing understanding of immunological processes, proinflammatory messengers and the function of regulatory T-cells should also be understood as a basis for the future treatment of sequelae after aneurysmal SAH. Further scientific efforts should aim in this direction.

5. Conclusion

Since higher serum levels of nimodipine might be achieved by intravenous compared to oral administration, it was to be feared that in clinical application the subsequent change to oral medication could be associated with an increased risk of cerebral vasospasm.

Our results suggest that switching from an initial intravenous nimodipine to oral therapy is safe and is neither associated with clinically relevant increases in TCD velocities nor other clinically relevant events.

An oral administration of nimodipine might allow earlier transfer of clinically stable patients on non-monitoring wards and sooner access to rehabilitation. A standardized assessment algorithm to monitor those patients could be helpful - this work therefore gives a suggestion.

In particular, cerebral vasospasm as a complication of aneurysmal SAH was highlighted. It is of great importance to recognize the multifactorial development of cerebral vasospasm and its clinically apparent consequence, the DCI, which could lead to new therapeutic options.

The detailed explanation of the topic of cerebral vasospasm suggests that the often poor outcome in aneurysmal SAH patients is not only determined by the occurrence of cerebral vasospasm itself and the question arises, if additional anti-inflammatory or immune modulating measures could be beneficial.

6. Zusammenfassung (Version auf Deutsch)

Die intravenöse Verabreichung des Calciumcanalblockers Nimodipin zur Behandlung und Prophylaxe von zerebralen Vasospasmen im Falle der aneurysmatischen SAB könnte zu höheren Serumspiegeln dieses Wirkstoffs führen, als eine orale Verabreichung, so dass zu befürchten war, dass der Wechsel auf eine rein orale Gabe mit einem erhöhten Risiko für zerebrale Vasospasmen verbunden ist. Unsere Ergebnisse legen nun nahe, dass die Umstellung von einer initialen intravenöse auf eine orale Nimodipingabe sicher ist und weder mit klinisch relevanten Erhöhungen der TCD-Geschwindigkeiten noch mit anderen klinisch relevanten Ereignissen assoziiert ist.

Eine orale Verabreichung von Nimodipin könnte eine frühere Verlegung von klinisch stabilen Patienten auf nicht überwachende Stationen und einen schnelleren Zugang zur Rehabilitation ermöglichen. Ein standardisierter Bewertungsalgorithmus zur Überwachung dieser Patienten könnte hilfreich sein - hierfür wurde ein mögliches Modell angeführt. Insbesondere der zerebrale Vasospasmus als Komplikation der aneurysmatischen SAB wurde in dieser Arbeit näher beleuchtet. Es scheint von großer Wichtigkeit, die multifaktorielle Entstehungsweise des zerebralen Vasospasmus und seiner klinisch apparenten Folge, der DCI, zu verstehen - was im Weiteren neue Therapieoptionen aufzeigen könnte.

Letztlich legt die ausführliche Erläuterung des Themas zerebraler Vasospasmus nahe, dass das oft schlechte Outcome bei Patienten mit aneurysmatischer SAB nicht nur durch das Auftreten von zerebralen Vasospasmen bestimmt wird und es stellt sich die Frage, ob zusätzliche antiinflammatorische oder immunmodulierende Maßnahmen von Vorteil sein könnten.

7. List of abbreviations

ACA	Anterior cerebral artery
ACI	Internal carotid artery
ACOM	Anterior communicating artery
AHA	American Heart Association
ATP	Adenosine triphosphate
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.
BNI	Barrow Neurological Institute
BPI	Brain perfusion imaging
DAG	Diacylglycerol
CBF	Cerebral blood flow
cCT	Cranial computed tomography
CTA	Computed tomography angiography
CI	Cerebral infarction
CPP	Cerebral perfusion pressure
CSD	Cortical spreading depolarization
CSF	Cerebrospinal fluid
CT	Computed tomography
CTP	CT-perfusion imaging
CVP	Central venous pressure
DCI	Delayed cerebral ischemia
DSA	Digital subtraction angiography
EEG	Electroencephalogram
EVD	External ventricular drainage
GCS	Glasgow Coma Scale
i.a.	intraarterial
ICP	Intracranial pressure
ICU	Intensive care unit
IQR	Interquartile range
i.v.	intravenous
LD	lumbar drainage
MAP	Mean arterial pressure

MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRT	Magnetic resonance imaging
MTA	Medical technical assistant
NO	Nitric oxide
PCOM	Posterior communicating artery
PKC	Protein kinase C
RP	Resting membrane potential
SAB	Subarachnoidalblutung
SAH	Subarachnoid hemorrhage
SD	Standard deviation
TCD	Transcranial Doppler sonography
UC	Uncomplicated course
WFNS	World Federation of Neurological Societies Score

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9. Note of thanks

At this point, I would like to express my great gratitude to all the people involved who have supported me in the preparation of my doctoral thesis:

First of all, my thanks go to PD. Dr. Patrick Czorlich, my doctoral supervisor, for the supervision of this dissertation, the friendly support, the constant reliable exchange, the motivating words and the constructive criticism.

Furthermore, I would like to thank Dr. Jennifer Göttsche for the numerous meetings and discussions as well as the collegial communication.

I thank my brother Jonathan for his help with the graphical preparation of the image files.

Many thanks go to my parents for their constant encouragement during my studies.

And last but not least, I would like to thank my wife, who not only accompanied me throughout my studies, but also constantly encouraged and lovingly as well as constructively supported me on my way towards my dissertation.

10. Curriculum vitae

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11. Affidavit

I expressly affirm that I have written the thesis independently and without outside help, that I have not used any sources or aids other than those indicated by me, and that I have individually identified the passages taken verbatim or in substance from the works used according to edition (edition and year of publication), volume and page of the work used.

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I agree that my dissertation may be checked by the Dean's Office of the Faculty of Medicine using common plagiarism detection software.

frontiers in Neurology

ORIGINAL RESEARCH
published: 16 November 2021
doi: 10.3389/fneur.2021.748413

Safety and Clinical Effects of Switching From Intravenous to Oral Nimodipine Administration in Aneurysmal Subarachnoid Hemorrhage

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 28 July 2021
Accepted: 11 October 2021
Published: 16 November 2021

Citation:
Göttsche J, Schweingruber N, Groth JC, Gerloff C, Westphal M and Czorlich P (2021) Safety and Clinical Effects of Switching From Intravenous to Oral Nimodipine Administration in Aneurysmal Subarachnoid Hemorrhage. Front. Neurol. 12:748413. doi: 10.3389/fneur.2021.748413

Objective: Several guidelines recommend oral administration of nimodipine as vasospasm prophylaxis after aneurysmal subarachnoid hemorrhage (SAH). However, in clinical practice, the drug is administered orally and intravenously (i.v.), depending on clinical conditions and local treatment regimens. We have therefore investigated the safety and clinical effects of switching from i.v. to oral nimodipine therapy.

Methods: Patients with aneurysmal SAH between January 2014 and April 2018 and initial i.v. nimodipine therapy, which was subsequently switched to oral administration, were included in this retrospective study. Transcranial Doppler sonography (TCD) of the vessels of the anterior circulation was performed daily. The occurrence of vasospasm and infarction during the overall course of the treatment was recorded. Statistical level of significance was set to $p < 0.05$.

Results: A total of 133 patients (mean age 55.8 years, 65% female) initially received nimodipine i.v. after aneurysmal SAH, which was subsequently switched to oral administration after a mean of 12 days. There were no significant increases in mean flow velocities on TCD after the switch from i.v. to oral nimodipine administration regarding the anterior cerebral artery. For the middle cerebral artery, an increase from 62.36 to 71.78 cm/sec could only be detected in the subgroup of patients with infarction. There was no clustering of complicating events such as new-onset vasospasm or infarction during or after the switch.

Conclusions: Our results do not point to any safety concerns when switching nimodipine from initial i.v. to oral administration. Switching was neither associated with clinically relevant increases in TCD velocities nor other relevant adverse events.

Keywords: subarachnoid hemorrhage, Transcranial Doppler, delayed cerebral ischemia, vasospasm, nimodipine, norepinephrine, catecholamine

INTRODUCTION

Cerebral vasospasm (CVS) and delayed cerebral ischemia (DCI) remain common and severe complications after aneurysmal subarachnoid hemorrhage (SAH) and are jointly responsible for the high morbidity and mortality, which is still above 20% in recent publications (1–3). About 30% of all patients develop DCI in the course of SAH (4). The underlying pathophysiology is thought to be of multifactorial origin: In addition to angiographic vasospasm, cortical spreading depolarization, microthrombosis, microcirculatory dysfunction and neuro-inflammation have been investigated recently as factors causing DCI (5–9).

Due to sedation, repetitive neurological exams cannot be performed to assess clinical deterioration, therefore Transcranial Doppler sonography (TCD) can be used as one of several methods to obtain indication of vasospasms especially in large intracranial arteries (10–14).

A treatment of SAH patients with nimodipine was shown in several studies to be effective in reducing incidence of poor outcome and severe neurological deficits after aneurysmal SAH but showed no influence on the occurrence of CVS or DCI (15–18). Although the underlying neuroprotective mechanism of nimodipine is yet not fully understood a positive effect on the functional outcome of SAH patients has been confirmed (19, 20). Administration of nimodipine is a well-established treatment modality and can happen orally or intravenously (i.v.) (21).

Based on the strong study evidence and current guideline recommendations, nimodipine should be given p.o. whenever possible (15–18, 22). However, in the acute phase, many patients cannot take the oral medication. There are considerations as to whether oral administration in analgosedated patients could result in lower bioavailability compared to i.v. administration (23, 24). It has therefore become clinical practice to administer the drug intravenously in the acute phase.

In a recent retrospective analysis <50% of all patients on oral nimodipine therapy received the full dose as a consequence of its blood pressure lowering effect, which should be avoided to prevent cerebral infarctions (25). This side effect of nimodipine counteracts the desired induced hypertension, forcing an intermittent interruption, lowering dose of application or concomitant intravenous administration of norepinephrine is often necessary.

TABLE 1 | Patient characteristics.

	UC	CVS	CI	CVS+CI	*p*-value
Number of patients (%)	57 (42.9)	30 (22.6)	19 (14.3)	27 (20.3)	
Sex—no. (%)					0.30
Male	22 (38.6)	7 (23.3)	9 (47.4)	8 (29.6)	
Female	35 (61.4)	23 (76.7)	10 (52.6)	19 (70.4)	
Age—mean (sd)	56.5 (14)	54.1 (13.4)	59.2 (13.4)	55.1 (13.9)	0.62
Localization of aneurysm (Circulation)—no. (%)					0.02
Anterior	39 (68.4)	20 (66.7)	10 (52.6)	25 (92.6)	
Posterior	18 (31.6)	10 (33.3)	9 (47.4)	2 (7.4)	
Hunt & Hess grade—no. (%)					0.79
1	12 (21.1)	4 (13.3)	5 (26.3)	5 (18.5)	
2	18 (31.6)	11 (36.7)	4 (21.1)	6 (22.2)	
3	9 (15.8)	8 (26.7)	4 (21.1)	6 (22.2)	
4	6 (10.5)	5 (16.7)	1 (5.3)	3 (11.1)	
5	12 (21.1)	2 (6.7)	5 (26.3)	7 (25.9)	
Fisher grade—median (IQR)	4.0 (±1.0)	4.0 (±1.0)	4.0 (±0.5)	4.0 (±0.5)	0.86
WFNS grade—median (IQR)	1.5 (±3.2)	2.0 (±2.8)	1.0 (±4.0)	2.5 (±3.8)	0.81
Initial GCS—median (IQR)	15.0 (±9.0)	14.0 (±3.5)	14.0 (±6.0)	13.0 (±8.5)	0.56
Pre-existing conditions—no. **(%)**					
Arterial hypertension	22 (38.6)	13 (43.3)	9 (47.4)	10 (37.0)	0.88
Alcohol abuse	5 (8.8)	1 (3.3)	0	0	0.20
Chronic headache	3 (5.3)	4 (13.3)	2 (10.5)	3 (11.1)	0.61
Diabetes mellitus	2 (3.5)	0	0	1 (3.7)	0.62
Cardiovascular disease	8 (14.0)	3 (10.0)	3 (15.8)	4 (14.8)	0.93
Smoking	13 (22.8)	6 (20.0)	5 (26.3)	6 (22.2)	0.97
Platelet aggregation inhibitors in premedication—no. (%)	32 (56.1)	11 (36.7)	12 (44.4)	16 (84.2)	0.13
Stay on ICU (days)—mean (sd)	17.5 (10.8)	19.2 (7.8)	24.3 (12.3)	18.7 (9.2)	0.05
Outcome—no. (%)					0.67
Deceased	9 (15.8)	3 (10)	6 (22.2)	3 (15.8)	
Survived	48 (84.2)	27 (90)	21 (77.8)	16 (84.2)	

GCS, Glasgow Coma Scale; ICU, Intensive Care Unit; IQR, Interquartile Range; sd, Standard Deviation; WFNS, World Federation of Neurosurgical Societies.

The intravenous administration of nimodipine therefore represents an alternative and has been investigated in several studies in the past due to its relevance (26–28). The aim of this analysis was to systematically evaluate our clinical observations of whether neurological and intensive care parameters change immediately due to the change from i.v. to oral administration in the course of the disease with a special focus on the measured blood flow velocity in TCD and the dosage of norepinephrine. If significant differences were to be found, this could be a basis for further investigations, since randomized data are not available at present.

The aim of this analysis was to evaluate our clinical observations of whether neurological and intensive care parameters change directly as a result of switching from i.v. to oral administration in the course of disease, focusing on measured blood flow velocity in TCD and norepinephrine dosing.

TABLE 2 | Flow velocities values pre and post nimodipine switch.

Subgroup	Pre in cm/sec mean (sd)	Post in (cm/sec) mean (sd)	*p*-value
ACA			
Overall population	64.83 ± 27.91	64.57 ± 22.75	0.93
UC	58.68 ± 22.26	62.24 ± 24.11	0.38
CVS	72.89 ± 34.43	66.00 ± 22.79	0.30
CI w/o CVS	60.40 ± 29.88	63.80 ± 19.14	0.45
CVS+CI	66.56 ±23.12	67.50 ± 23.31	0.90
MCA			
Overall population	83.82 ± 37.54	81.82 ± 30.53	0.48
UC	74.87 ± 31.73	72.87 ± 30.26	0.63
CVS	98.88 ± 46.19	92.97 ± 29.82	0.34
CI w/o CVS	62.36 ± 22.43	71.78 ± 22.26	<0.01
CVS+CI	93.80 ± 30.05	90.45 ± 30.36	0.67

ACA, Anterior Cerebral Artery; CVS, Cerebral Vasospasm; CI, Cerebral Infarction; MCA, Middle Cerebral Artery; Pre = 1 day before nimodipine iv switch to oral administration, Post = first day of oral nimodipine administration, sd, Standard Deviation; UC, Uncomplicated Course; w/o, Without.

MATERIALS AND METHODS

Study Population

Only patients admitted with aneurysmal SAH between January 2014 and April 2018 and initial i.v. nimodipine therapy over at least 48 h, which was subsequently switched to oral administration, were included in this retrospective single center study, resulting in 133 of 299 SAH patients available for further analysis (for details see **Supplementary Figure 1**). Basic clinical characteristics of our study population including clinical parameters and SAH-relevant events on intensive care unit (ICU) at admission and during hospitalization as well as medical history were collected. Data collection included demographic information, aneurysm location, information on antiplatelet aggregation medication, pre-existing conditions and distinct clinical evaluation scores (Glasgow Coma Scale, Hunt & Hess grading system, WFNS grading system, Fisher score). The drug doses were extracted from the intensive care unit's electronic documentation system (Integrated Care Manager, Dräger Medical Deutschland GmbH, Lübeck, Germany).

This study was conducted according to the Declaration of Helsinki, local and institutional laws and was reported to the local ethical committee (No. WF-039/20). Written informed consent was waived for this kind of study.

Treatment Protocol

All patients were treated according to common guidelines and as previously described (22). Intravenous nimodipine was administered when it was expected that the patient would remain sedated for a longer period of time, primarily in higher-grade SAH patients or patients suffering severe complications like rebleeding, or when oral medication was not safely absorbed enterally due to nausea and vomiting. After initiation of i.v. nimodipine (Nimotop S, Bayer Vital, Leverkusen, Germany) therapy with a continuous infusion rate of 2 mg/h, it was continued depending on the level of analgosedation or already evident vasospasms or perfusion deficits. The switch to enteral administration was then made with 60 mg orally 4 h apart. In patients unable to swallow but expected enteral absorption, tablets were crushed and washed down a nasogastric tube with normal saline (23, 29).

If vasospasm, perfusion deficits of one hemisphere or territorial, or neurological deficits were detected, and vasospasm was confirmed via digital subtraction angiography (DSA), i.a. spasmolysis with nimodipine was applicated via a microcatheter as rescue-therapy.

Detection and Definition of Vasospasm and Delayed Cerebral Ischemia

Transcranial Doppler sonography of the anterior cerebral arteries (ACA) as well as the middle cerebral arteries (MCA) was performed daily beginning on the first day after admission via the transtemporal window. All measurements were performed with the same device (DWL Multi-Dop T Digital, Compumedics Germany GmbH, Singen, Germany) using a 2 MHz frequency ultrasound probe. The measurements were mainly carried out by the same trained medical technical assistant to avoid examiner-dependent bias. Mean flow velocities were recorded. Vasospasm was suspected by TCD if the mean flow velocity in the MCA was above 140 cm/s and above 120 cm/s in the ACA, respectively. In case of TCD suspicion of vasospasm we perform according to our local treatment protocol a computer tomography (CT) -scan, including computed tomography angiography (CTA) and CT-perfusion imaging (CTP). The occurrence of vasospasm and DCI was defined according to criteria published by Vergouwen et al. (30). In cases with proven high-grade vasospasm in CTA and/or a perfusion deficit in CTP a digital subtraction angiography (DSA) was then carried out (30).

Definition of Subgroups

Depending on the neurological parameters and TCD, the following subgroups were defined to assess whether there were differences within these groups, which would further increase

significance: (a) patients who had neither vasospasms nor infarctions, patients in whom either (b) vasospasms or (c) infarctions could be detected and (d) patients in whom both were present.

Data Analysis

Medication was extracted as flowrate of a continuous application (nimodipine and norepinephrine) or as time of administration (nimodipine oral). Cumulative drug dosage over 24 h was calculated to perform possible correlations with measured TCD values (typically one per day). Quantitative variables were described as mean and standard deviation (SD), qualitative variables are outlined as number and percentage. The cumulative oral or i.v. dosage of nimodipine per day was used to characterize the phases of i.v. or oral administration of nimodipine. Between a dosage of 200 mg nimodipine orally and 10 mg i.v. per day administration was defined as oral. Values in between ($\leq$200 mg/d orally and $>$10 mg/d nimodipine i.v.) were defined as overlap. I.v. administration was defined only if oral nimodipine was not administered. Only the switch from nimodipine i.v. to oral was considered.

Some patients had a longer overlapping time (max. 48 h) these values are depicted separately and not used for paired analysis. In some patients two phases of changes were presented, in these cases the last change was taken. We performed a gathered analysis of values from ACA and MCA and also of all values combined to show that even when combining values, no significant change was observed.

Statistical analysis of the data was performed by a univariate analysis using chi-squared tests, independent-samples Kruskal-Wallis tests or ANOVA tests depending on the scale of the measurements and equality of variances.

To examine correlations between the parameters we calculated the linear regression coefficient. The level of statistical significance was set at $p < 0.05$. To visualize parameters from the digital patient record, the time since ICU admission was analyzed by day and the mean (point) and standard error of the mean (error bars) were calculated. Data transformation, calculation and visualization was done in R (version 3.6.3 main

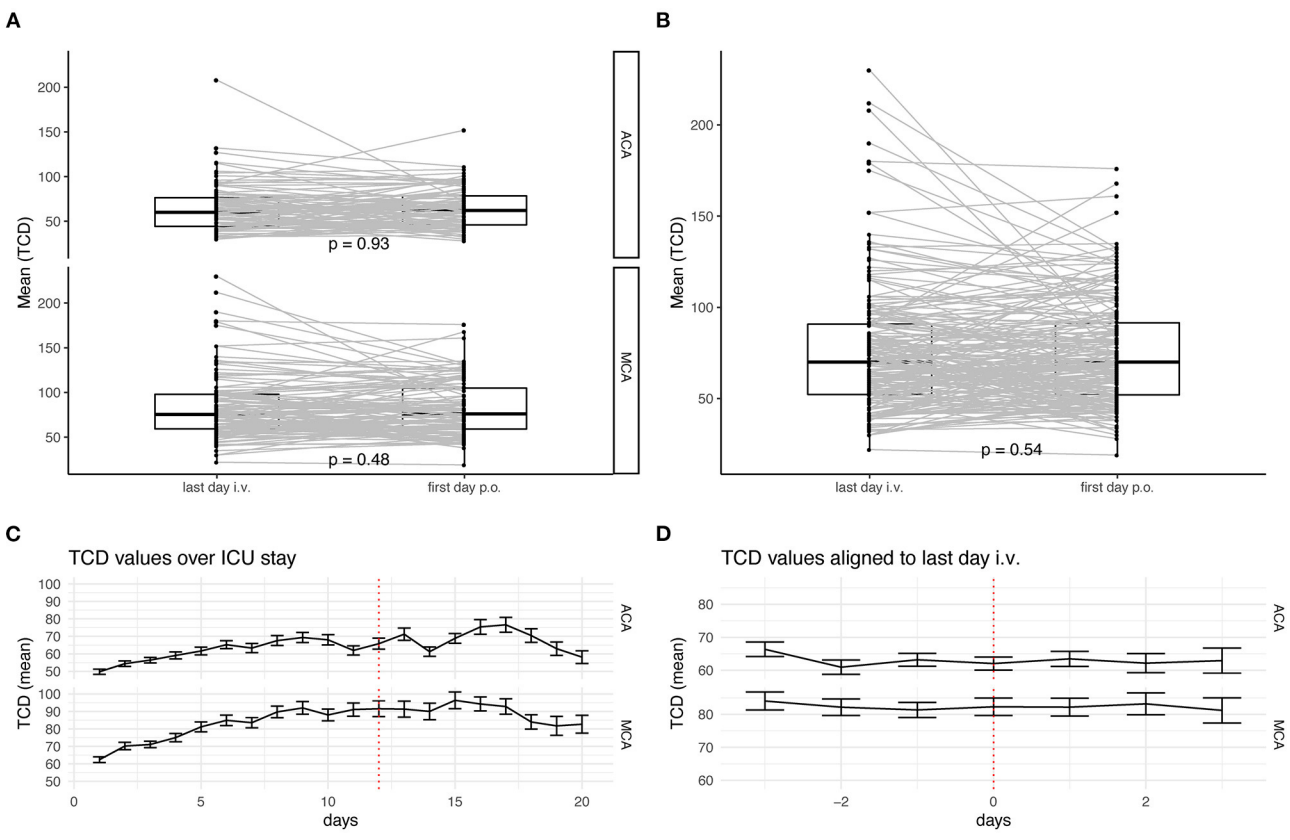

FIGURE 1 | Analysis of TCD-values during the switch of the route of administration. **(A)** TCD values are measured longitudinal in patients. Only patients with consecutive values before and after switching the route of administration of nimodipine are depicted. Values for A. cerebri anterior (upper) and A. cerebri media (lower) are depicted separately. **(B)** All TCD values independent of their circulation are depicted. The lower and upper hinges of the boxplots correspond to the first and third quartile of all values. The whiskers represent the 1.5 inter quantile range (IQR). Dots show each value and grey lines connect individual patients' measurements. Statistical analysis was performed with paired *t*-test. **(C)** Mean TCD values are shown over the first 20 days of ICU stay for A. cerebri anterior (upper) and A. cerebri media (lower). Error bars represent the standard deviation. **(D)** Mean TCD values aligned to the individual switch of the route of administration. Whiskers represent. Error bars represent the standard deviation.

packages: dplyr, tidyverse, stringr, ggplot2, ggpubr). For final composition of Figures Adobe Illustrator was used (Adobe Inc., San José, USA; Version 24.3).

RESULTS

A total of 133 patients initially received nimodipine i.v. after aneurysmal SAH, which was subsequently switched to oral administration after a mean of 11.7 ± 5.78 days. Forty six male and 87 female patients with a mean of 56 ± 13.7 years of age were included in this study. The aneurysms most frequently causing a SAH were situated in the anterior circulation (70.7%). Vasospasms were detected via CTA, CTP and DSA imaging in 30% of cases. Besides the detection of vasospasms 20.3 % of patients showed an infarction on imaging. In 14.3% of patients an infarction could be documented without any prior detection of vasospasm. 42.9% of the patients were classified as uncomplicated course of SAH since neither vasospasms nor infarctions occurred.

Patient cohorts were further divided and defined according to these findings: Patients who had an uncomplicated course (UC) represented the major group with 57 patients. CVS occurred in 30 cases (22.6%), 19 patients (14.3%) suffered from cerebral infarction without CVS (CI), and CVS+CI occurred in 27 cases (20.3%), **Table 1**.

Mean flow velocities of the MCA 24 h before switching to oral administration were 83.82 cm/s (MCA) and 64.83 cm/s (ACA).

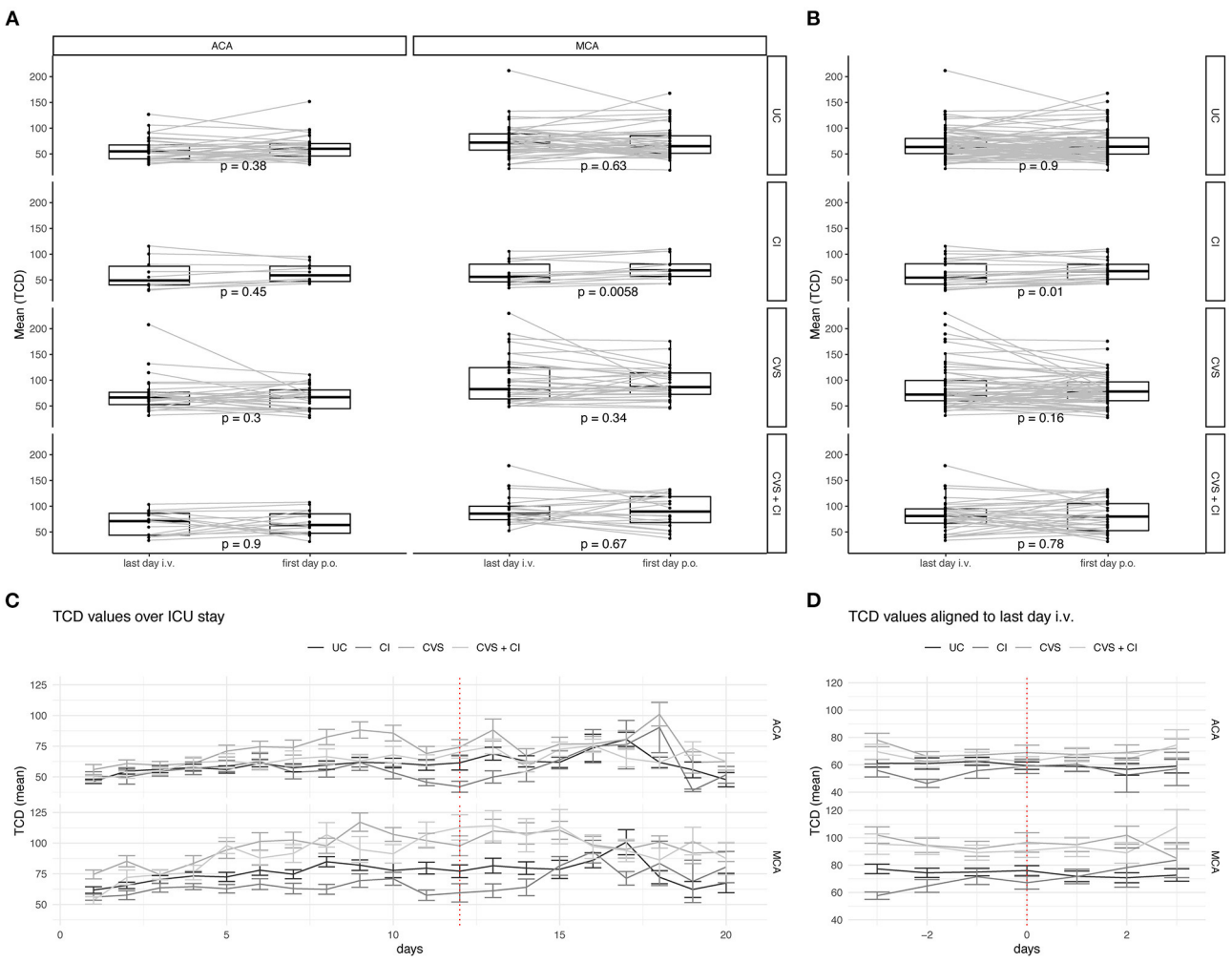

FIGURE 2 | Analysis of TCD-values of subgroups during the switch of the route of administration. TCD values are measured longitudinal in all patients during the ICU stay. Grouping is done according to radiological findings: Uncomplicated Course (UC), Cerebral Infarction (CI), Cerebral Vasospasms (CVS), and Cerebral Vasospasm and Cerebral Infarctions (CVS + CI). **(A)** Only patients with consecutive values before and after switching the route of administration of nimodipine are depicted. Values for A. cerebri anterior (left) and A. cerebri media (right) are depicted separately. **(B)** All TCD values independent of their circulation are depicted. The lower and upper hinges of the boxplots correspond to the first and third quartile of all values. The whiskers represent the 1.5 inter quantile range (IQR). Dots show each value and grey lines connect individual patients' measurements. Statistical analysis was performed with paired *t*-test. **(C)** Mean TCD values are shown over the first 20 days of ICU stay for A. cerebri anterior (upper) and A. cerebri media (lower). Error bars represent the standard deviation. **(D)** Mean TCD values aligned to the individual switch of the route of administration. Whiskers represent. Error bars represent the standard deviation.

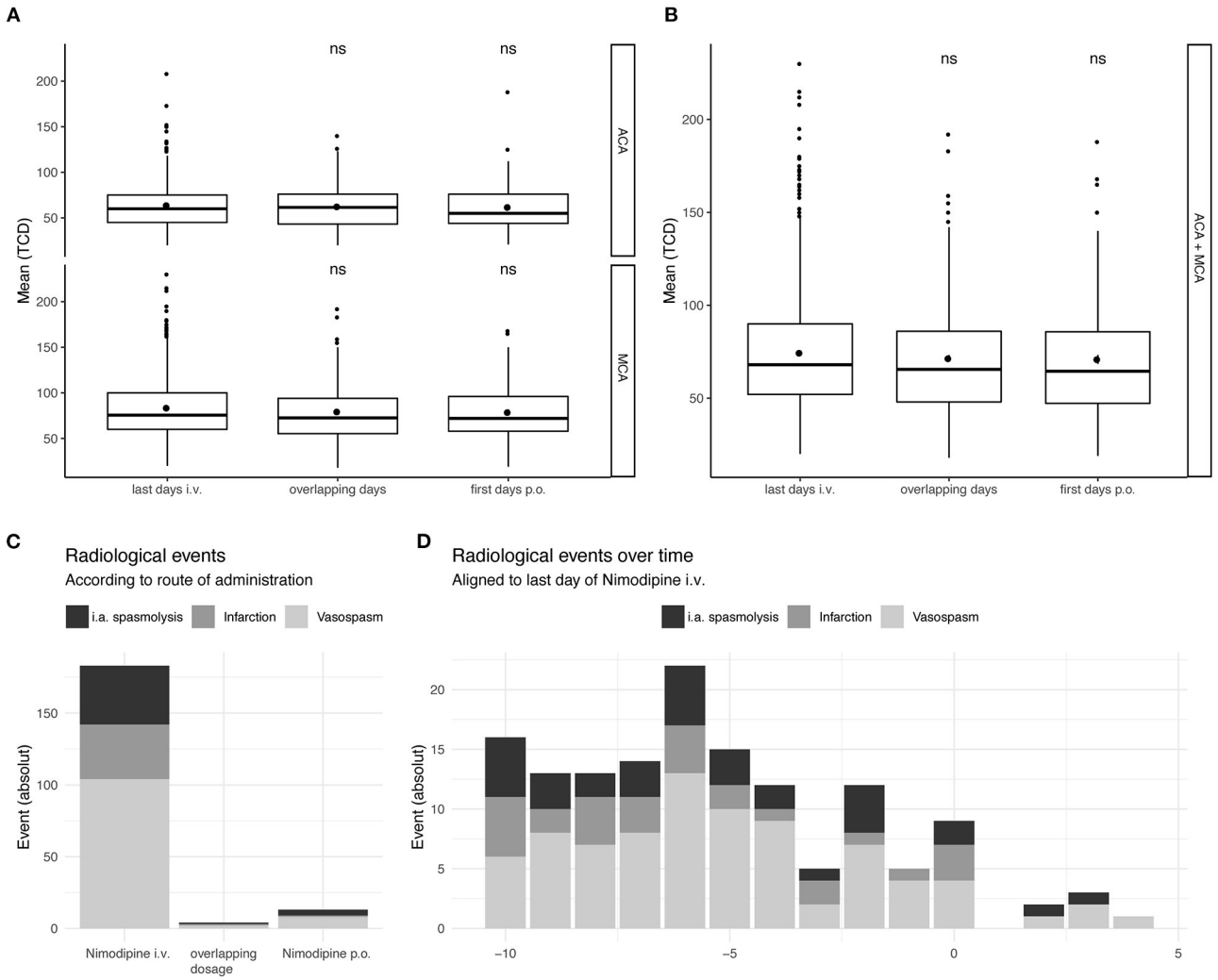

FIGURE 3 | Temporal resolution of complications in subgroups in relation to the timing of the switch. Taking all measured TCD values in account of all patients included in the study not only longitudinal but all values were considered. TCD values on the last 2 days of Nimodipine iv. and the first 2 days of oral administration only were depicted, together with overlapping dosages. **(A)** Values for A. cerebri anterior (upper) and A. cerebri media (lower) are depicted separately. **(B)** All TCD values independent of their circulation are depicted. The lower and upper hinges of the boxplots correspond to the first and third quartile of all values. The whiskers represent the 1.5 inter quantile range (IQR). Statistical analysis was performed with unpaired *t*-test compared to the last day of i.v. administration. **(C)** Absolute amount of the radiological events are show according to the administered drug. **(D)** Radiological events over all the ICU stay (Absolute numbers). ns, not significant.

On the first day after the switch mean flow velocities on TCD were 81.82 and 64.57 cm/s, respectively. This analysis was also performed depending on the occurrence of complications and examined for the above-mentioned subgroups.

There were no significant increases in mean flow velocities on TCD on the first day after switching the route of administration to oral administration in either subgroup of patients except for MCA in the CI group (**Table 2**). Mean flow velocities of the MCA in the UC group were 72.87 and 90.45 cm/s in the CVS+CI group. With respect to the ACA, mean values of 62.24 cm/s (UC) and 67.50 cm/s (CVS+CI) were recorded.

An analysis of the last day of i.v. administration of nimodipine vs. the first day of the full oral dose was performed. There were no significant changes in the flow velocities of the middle and anterior cerebral arteries (**Figures 1A,B**). The mean TCD values measured in the course of time during the intensive care stay and especially during the switch are shown in **Figures 1C,D**. For a more detailed description of the heterogeneous collective, the above-mentioned subdivision into subgroups was applied; in addition, the values for ACA and MCA are listed separately (**Figure 2**). There were no significant increases after switching the type of administration.

No significant increase in flow velocities occurred during the switch or on the day after the switch compared to the day before the switch (last day i.v.) (**Figures 3A,B**). In none of the groups with complications (CVS, CI and CVS+CI) was there a significant increase in flow velocities during the switch or on the days after the switch compared to the days before the

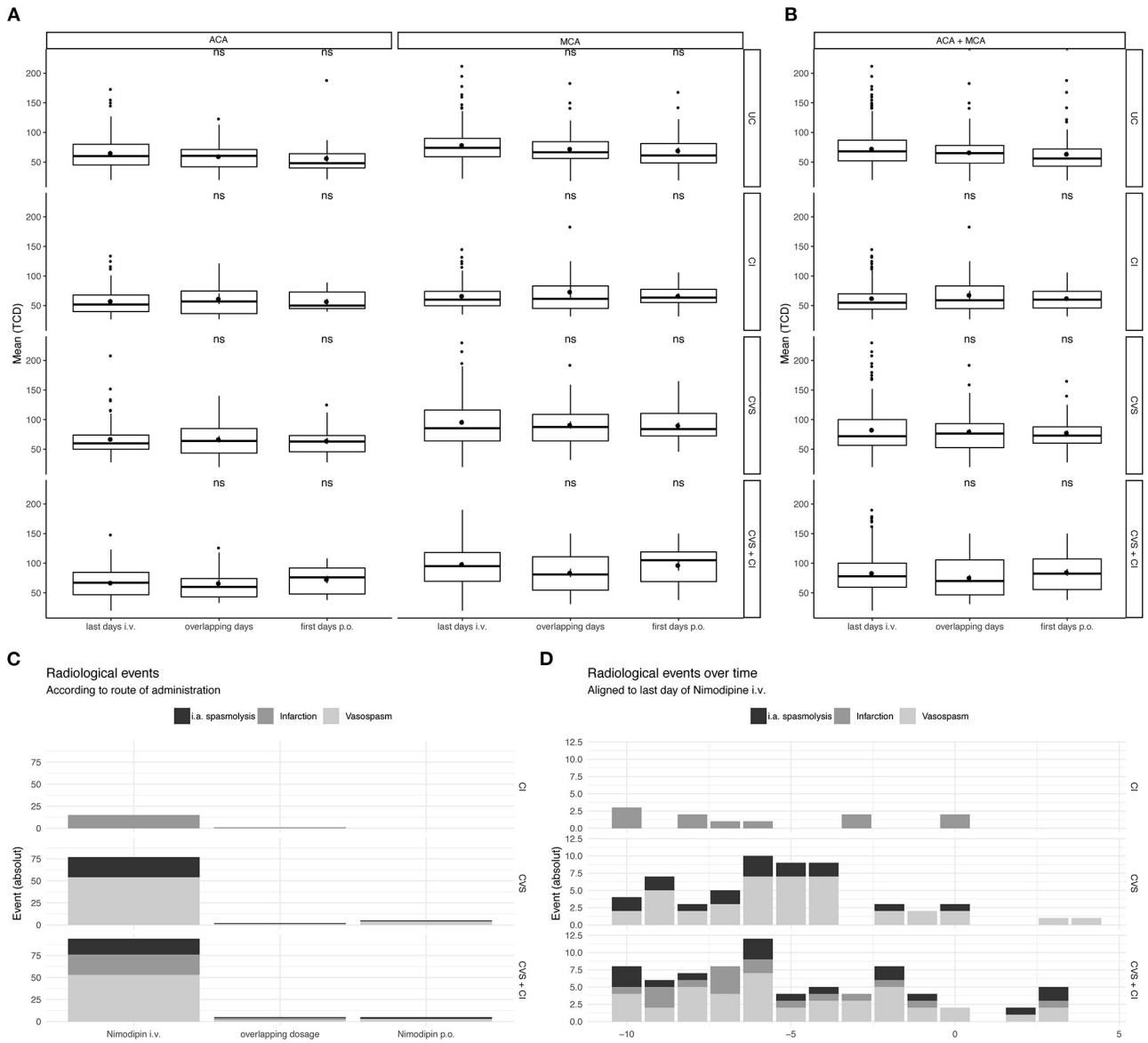

FIGURE 4 | Temporal resolution of complications in subgroups in relation to the timing of the switch. Taking all measured TCD values in account of all patients included in the study not only longitudinal but all values were considered. TCD values on the last 2 days of Nimodipine iv. and the first 2 days of oral administration only were depicted, together with overlapping dosages. Grouping is done according to radiological findings: Uncomplicated Course (UC), Cerebral Infarction (CI), Cerebral Vasospasms (CVS), and Cerebral Vasospasm and Cerebral Infarctions (CVS + CI). **(A)** Values for A. cerebri anterior (upper) and A. cerebri media (lower) are depicted separately. **(B)** All TCD values independent of their circulation are depicted. The lower and upper hinges of the boxplots correspond to the first and third quartile of all values. The whiskers represent the 1.5 inter quantile range (IQR). Statistical analysis was performed with unpaired *t*-test compared to the last day of i.v. administration. **(C)** Absolute amount of the radiological events are show according to the administered drug. **(D)** Radiological events over all the ICU stay (Absolute numbers). ns, not significant.

switch (last day i.v.) (**Figures 4A,B**). In an unpaired analysis, the combination of flow velocities of ACA and MCA showed significantly lower flow velocities among the uncomplicated courses on the first day after the switch (**Figure 3B**). No further significant changes on TCD during the switching period were found (**Figures 3A,B**).

In a next step, we examined the time course of the complications that occurred in relation to the timing of oralization. There was no accumulation of complications (CVS, CI) after or during the switch of the route of administration (**Figures 3C,D**, **4C,D**): During the intravenous administration phase, 93 events occurred in the CVS+CI group. Of these, 18 were intraarterial spasmolyses with locally administered nimodipine. After the switch, 8 events occurred in the same group, of which 3 were intraarterial spasmolyses with locally administered nimodipine.

Cerebral infarctions were mainly detected in the first 10 days of ICU stay, which is in line with detection of CVS. Within the first 10 days, 37 of a total of 46 cerebral infarctions occurred. Furthermore, 93 of a total of 124 cerebral vasospasms occurred and 35 of a total of 50 i.a. spasmolyses were performed within the first 10 days.

Systemic mean arterial pressure remained stable during the switch (not shown). Furthermore, the mean catecholamine dose decreased significantly in all groups after the switch. Before the switch the dose ranged from 7 to 13 mg norepinephrine/day (depending on the group, **Table 3**) compared to 4–8 mg/day after the switch.

To further address the changes of nimodipine dosage and their influence to the underlying changes in flow velocities correlation analyses were performed (**Figure 5**).

While i.v. nimodipine shows no relevant correlation, oral nimodipine shows a negative correlation coefficient in the UC- and CVS group.

DISCUSSION

The evidence for oral administration of nimodipine is derived from randomized-controlled trials. However, both intravenous and oral administration of nimodipine are common practice and, in addition to intra-arterial rescue therapy, have a relevant role in everyday clinical practice (31). Some studies showed no significant difference in terms of plasma concentration or efficacy achieved when comparing oral with intravenous administration (32–34). The need to administer norepinephrine, which often accompanies intravenous administration, initially keeps patients in the ICU. Transfer to a peripheral ward is therefore often only possible after oral administration and thus absence of catecholamines. Hence the desire for a rapid switch to oral administration. Despite the known data with regard to bioavailability, to the best of our knowledge, studies investigating parameters at the point of switch from intravenous to oral nimodipine administration are completely missing in the literature (22, 23).

The discussed lower oral bioavailability of nimodipine, especially in analgosedated patients, as well as the frequent blood pressure-related interruption of oral administration make i.v. administration of the drug a valid and common alternative (23–25). Sandow et al. were able to demonstrate that low blood pressure often leads to dose reductions or interruption of oral dosing, which may be associated with unfavorable outcome (25). When administered intravenously, there is a reduced risk of lower bioavailability in sedated patients. Intravenous nimodipine therapy is therefore often used initially in the intensive care therapy of SAH patients followed by a switch to oral administration in the later, more stabilized phase.

In the context of this clinically relevant topic, we were able to show that almost no significant change in flow velocities or incidence of negative clinical events occurred after the switch. Although flow velocities in the CI group increase significantly on the first day after the switch (**Table 2**), this is apparently clinically not relevant as there seems to be no clustering of adverse events (**Figure 4D**).

Since our patient cohort is heterogeneous including patients with complications as well as uncomplicated courses, all parameters in the subgroups in which complications occurred were systematically examined to increase the sensitivity of the analyses.

TABLE 3 | Norepinephrine dose around nimodipine switch [mg/day].

	Pre mean (sd)	Post mean (sd)	*p*-value
UC	9 (7)	4 (5)	<0.0001
CI	7 (7)	4 (3)	0.03
CVS+CI	13 (10)	8 (6)	<0.0001

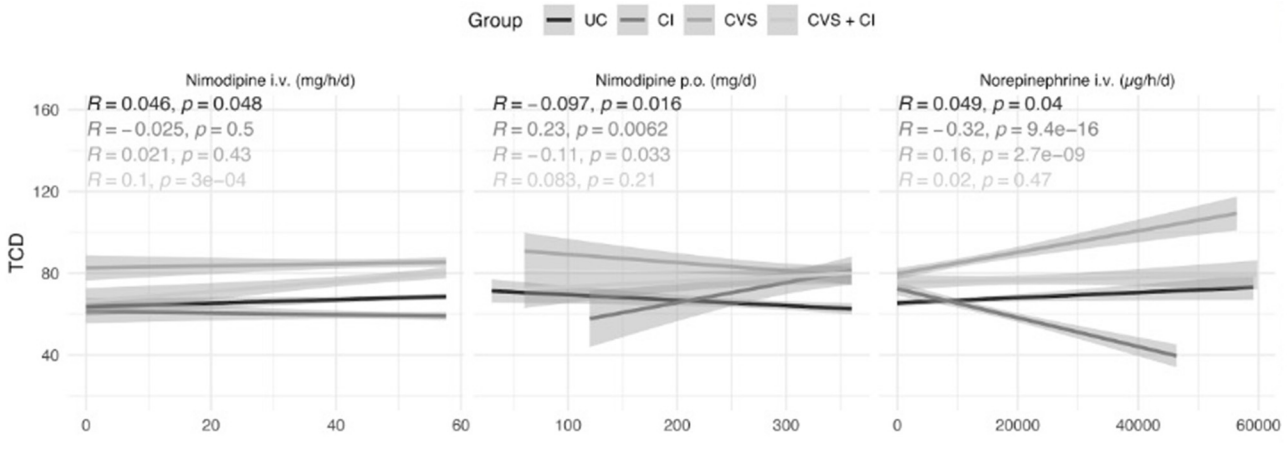

FIGURE 5 | Correlation of Transcranial Doppler Sonography to oral and i.v. nimodipine. Groups: Red line—uncomplicated; green line Infarcts, blue line vasospasms, and purple line vasospasms and infarcts. To unveil dosage effects correlation analysis were done. All TCD values are depicted and correlated to the Nimodipine iv., oral and Norepinephrine cumulative dosage over 24 h. Linear regression line with the according standard error are depicted for the defined groups. Pearson correlation coefficient and the according *p*-value are shown in the upper left of the plots.

Even though we explicitly looked into groups with complications and compared them with uncomplicated courses, we found no differences.

It should be noted that the switch was performed at a mean of 12 days after admission to the ICU and thus at a time when the risk for vasospasm is still present but decreasing (35, 36).

This study has a number of limitations, particularly its retrospective, single-center design. Despite the relatively small sample size, demographics correspond well with other SAH cohorts and epidemiological data.

The potential benefit of initial intravenous nimodipine therapy is still unclear and will have to be investigated in prospective studies. Our data and the considerations for intravenous administration may be relevant for studies comparing standard nimodipine therapy with an investigational drug like the NEWTON trial (37).

In conclusion, we found no indication of safety concerns when switching from initial intravenous nimodipine administration in the acute phase to subsequent oral administration. The switch was neither associated with clinically relevant increases in TCD-velocities nor with other relevant adverse events.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hamburg Ethical Committee Weidestr. 122 b 22083 Hamburg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JG supervised the study, designed the study question, interpreted the data, and drafted the manuscript. NS conceived the study question and analyzed and interpreted the data. JCG collected the data. CG contributed to the data interpretation. MW helped to interpret the data and conceive the study questions. PC contributed to the overall design of the study, supervised the study, conceived the study question, designed the analysis plan, and analyzed and interpreted the data. All authors revised the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.748413/full#supplementary-material

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