Neurosurgical Review (2019) 42:463–469
https://doi.org/10.1007/s10143-018-0986-5

ORIGINAL ARTICLE

The evolution of invasive cerebral vasospasm treatment in patients with spontaneous subarachnoid hemorrhage and delayed cerebral ischemia—continuous selective intracarotid nimodipine therapy in awake patients without sedation

Andrej Pala[1] · Max Schneider[1] · Christine Brand[1] · Maria Teresa Pedro[1] · Yigit Özpeynirci[2] · Bernd Schmitz[2] · Christian Rainer Wirtz[1] · Thomas Kapapa[1] · Ralph König[1] · Michael Braun[2]

Received: 16 February 2018 / Revised: 1 May 2018 / Accepted: 17 May 2018 / Published online: 26 May 2018

Abstract

Cerebral vasospasm (CV) and delayed cerebral ischemia (DCI) are major factors that limit good outcome in patients with spontaneous subarachnoid hemorrhage (SAH). Continuous therapy with intra-arterial calcium channel blockers has been introduced as a new step in the invasive treatment cascade of CV and DCI. Sedation is routinely necessary for this procedure. We report about the feasibility to apply this therapy in awake compliant patients without intubation and sedation. Out of 67 patients with invasive endovascular treatment of cerebral vasospasm due to spontaneous SAH, 5 patients underwent continuous superselective intracarotid nimodipine therapy without intubation and sedation. Complications, neurological improvement, and outcome at discharge were summarized. Very good outcome was achieved in all 5 patients. The Barthel scale was 100 and the modified Rankin scale 0–1 in all cases at discharge. We found no severe complications and excellent neurological monitoring was possible in all cases due to patients' alert status. Symptoms of DCI resolved within 24 h in all 5 cases. We could demonstrate the feasibility and safety of selective intracarotid arterial nimodipine treatment in awake, compliant patients with spontaneous SAH and symptomatic CV and DCI. Using this method, an excellent monitoring of neurological function as well as early detection of other complications is possible. It might be an important step in the risk reduction of invasive CV therapy to improve the outcome with CV and DCI after SAH in selected patients.

Keywords Subarachnoid hemorrhage · Vasospasm · Nimodipine · Continuous intra-arterial infusion · Delayed cerebral ischemia

Introduction

Despite the fact that the mortality of spontaneous subarachnoid hemorrhage (SAH) decreased within the last century, vasospasm still seems to be one of the most relevant factors which influence patients' outcome [1]. Delayed cerebral ischemia (DCI) after SAH accounts for up to 30% of new neurological deficits [2, 3]. The detection of cerebral vasospasm (CV) as a possible cause of DCI and its further treatment is crucial in the treatment path of SAH patients [2]. As a calcium channel blocker, nimodipine is the only pharmacological agent that has been shown to have a positive effect on outcome in CV [1]. In patients with refractory CV, invasive endovascular methods, such as balloon angioplasty, temporary deployment of retrievable intracranial stents, as well as repeatedly or continuous selective intra-arterial injection of calcium channel blockers could be considered [4–7]. Because of relatively short half-life of nimodipine, repeated superselective intra-arterial injections are often needed. Therefore, continuous selective intracarotid application of calcium channel blockers (nimodipine) has been introduced as a treatment option [8–11]. A microcatheter is deployed into each internal carotid artery via transfemoral access. This necessitates leaving an introducer sheath and a large-bore catheter in the groin and aorta. In order to avoid unintentional dislocation of microcatheters from the internal carotid arteries, intubation and sedation of these patients has been generally accepted.

✉ Andrej Pala
andrej.pala@uni-ulm.de

[1] Department of Neurosurgery, University of Ulm, Ludwig Heilmeyerstr. 2, 89312 Günzburg, Germany

[2] Department of Neuroradiology, University of Ulm, Ludwig Heilmeyerstr. 2, 89312 Günzburg, Germany

Consequently, direct monitoring of neurological function is not possible under these circumstances. Multimodal monitoring including transcranial Doppler sonography as well as partial oxygen brain tissue pressure (ptO2) monitor the treatment effect and the course of the disease only indirectly. To improve the invasive vasospasm therapy monitoring and its effect on neurological deficits, continuous selective intracarotid nimodipine application without general anesthesia was proposed in compliant patients with refractory cerebral vasospasm and DCI after SAH, if all other less invasive treatment options did not result in improvement of neurological deficits.

To our knowledge, this is the first report describing the feasibility of continuous intra-arterial vasodilator therapy in awake patients.

Methods

This study comprises a cohort of 67 patients with SAH who underwent endovascular treatment of CV with continuous selective intracarotid calcium channel blocker infusion. All patients sustained spontaneous SAH. Initial head CT and CT angiography were performed for detection of hydrocephalus and bleeding source. In the case of hydrocephalus, a ventricular drain was implanted and if an aneurysm responsible for bleeding had been identified, it was treated with either clipping or coiling within 24 h after admission to our hospital. The neurovascular team consisting of neurosurgeons and neuroradiologists was involved in the decision-making process throughout the whole treatment. In all symptomatic patients, induced hypertension and either oral or intravenous nimodipine were applied depending on the severity of CV identified with CT angiography and transcranial Doppler sonography (TCD). According to our protocol, induced hypertension (MAP ≥ 100 mmHg) and continuous intravenous therapy with nimodipine are indicated in the case of symptomatic CV and DCI. Except for neurological deterioration, relevant increase in TCD (> 120 cm/s or 30 cm/s/day) is used as a condition for CV definition. The increase of 30 cm/s/day is the most relevant parameter in this concern. The blood velocity of 120 cm/s without rapid progression or new focal neurological deficits results in closer observation and higher frequency of TCD. According to our local protocol, CT with CT-angiography and CT-perfusion is performed after initiation of the conservative measures. If CT-perfusion revealed perfusion delay and CTA confirmed CV despite maximal conservative management, DSA and intra-arterial continuous infusion of nimodipine via indwelling microcatheters in both internal carotid arteries were indicated. Awake patients with SAH and progressive CV and symptomatic DCI were eligible for the treatment without general anesthesia. This is a new therapy concept which has been started at our department since the end of 2017. Patients' neurological status and compliance were the main aspects that made the awake spasmolytic nimodipine therapy feasible. After severe CV was confirmed by digital subtractive angiography (DSA), a 6F guiding catheter (Envoy; Codman Neurovascular, Raynham, MA, USA) was inserted through a 6F introducer sheath (Terumo; Tokyo, Japan). Following that, bilateral microcatheters (Echelon 10; Covidien, Mansfield, MA, USA) were placed in the petrous part of the internal carotid artery. These were left in place, while the guiding catheter was pulled down to the aortic arch. The 6F introducer sheath was then fixated to the skin with two sutures. The extracorporal part of the guiding catheter was placed with a loop in that way, that its hemostatic valve pointed cranially, so that the microcatheters could be placed on the abdomen. It was padded with gauze swabs to prevent ulcers and secured with standard OPSITE® films which enabled a waterproof and transparent dressing enabling regular checks from outside.

Up to 2 mg nimodipine per hour were given continuously through the microcatheters and simultaneously, anticoagulation with full dose of low molecular heparin and daily oral 100 mg acetylsalicylic acid was administered during the intra-arterial therapy.

TCD was performed daily. Difference between blood flow velocity in TCD 24 h before intra-arterial therapy and directly before the procedure as well as before the procedure and 24–48 h after the beginning of the therapy was calculated. Duplex sonography and assessment of the microcatheter in the ICA to rule out dislocation or apposition thrombus or signs of vessel wall injury were performed routinely. Anti-factor Xa was measured for dose adjustment of low molecular weights heparins. Neurological examination was assessed at least 3 times daily. Nimodipine dose was adjusted according to the clinical findings and Doppler values. In the case of obvious neurological and sonographic improvement, intra-arterial nimodipine was stopped with overlapping intravenous administration of nimodipine. A CT scan with CT-angiography and -perfusion was performed 6 h later. If no relevant CV or significant improvement with no DCI in CT-perfusion was found, DSA was initiated and intra-arterial catheters were removed. The detailed monitoring of neurological status was documented. Nimodipine therapy was continued either intravenously or orally.

Results

Five patients who developed symptomatic CV were treated with continuous nimodipine infusion without sedation. In 2 cases, the continuous intra-arterial nimodipine infusion lasted for 7 days, in 1 for 10 days and in 2 cases even 15 days of intra-arterial nimodipine therapy were necessary. Demographic data as well as the aneurysm characteristics are summarized in Table 1. The initial symptoms of DCI in our patient group were new onset of speech disturbances in two patients, new onset of

progressive hemiparesis in two patients, and confusion followed by reduced state of consciousness in one patient. TCD confirmed significant increase in blood flow velocity. CT-perfusion confirmed significant perfusion delay in all patients.

Overall blood flow velocity in TCD showed direct response on intra-arterial nimodipine therapy, 24 to 48 h after initiation of treatment (Table 1).

One patient removed the intra-arterial catheter unintendedly after 7 days of treatment. In 1 case, a small local thrombus was found in the femoral artery after a treatment period of 15 days. Follow-up with daily Duplex sonography showed regression of thrombus without causing significant occlusion or thromboemboli. All patients achieved an excellent outcome at discharge without focal neurological deficit. No heparin- or nimodipine-related complications were documented. New neurological deficits induced by DCI resolved within 24 h in all cases. The Modified Rankin scale was 0–1 and the Barthel scale 100 at the discharge from the hospital.

Illustrative case

A 46-year-old female patient was admitted to our hospital with severe headache and nausea. She had a history of nicotine abuse and arterial hypertension. CT scan revealed SAH. According to Hunt & Hess scale, SAH was graded as I. According to the Fisher scale, it was graded as III. Initially, CSF drainage was renounced due to her good clinical status and missing signs of hydrocephalus in CT. Multiple aneurysms (left MCA, distal ICA and PCA; right ACA) were detected on CTA. Due to distribution pattern of SAH and greater size of aneurysms, the left-sided MCA and ICA aneurysms were identified as possible sources of bleeding. Both aneurysms were treated endovascularly (Fig. 1). No intraprocedural complications were documented. The patient was admitted to the ICU for further observation. Nimodipine therapy was initiated with starting dose of 6 × 60 mg orally. Four days after onset of SAH, bilateral increase of blood velocity in MCA and ICA was detected. Induced hypertension with mean arterial pressure of 100 mmHg was initiated. Simultaneously, according to our institutional protocol, nimodipine therapy was escalated from oral nimodipine to i.v. nimodipine, 2 mg/h. Despite these measures, a rapid clinical deterioration and progressive global aphasia occurred. Perfusion CT revealed perfusion delay within the left MCA and ACA territory (Fig. 2a). Furthermore, progressive macrovasospasm was detected on CTA and DSA (Figs. 2b and 3). The patient was considered being eligible for awake implantation of intracarotid microcatheters transfemorally (Fig. 4). The procedure was performed in local anesthesia. No complications occurred. Continuous intracarotid nimodipine therapy with up to 2 mg of nimodipine per hour was started. After few hours, the speech disturbance resolved completely. Transcranial Doppler sonography showed normal flow velocities in ICA and MCA on both sides during the next days. After 7 days of treatment, improvement of radiological macrovasospasm was found. New cerebral infarctions could be excluded. The intra-arterial nimodipine therapy was stopped, instead intravenous nimodipine was administered. The patient was discharged from hospital after 23 days without neurological deficit. Oral nimodipine was administered till 2 weeks after discharge and slowly reduced to none.

Discussion

We present a new option for invasive treatment of DCI and CV in patients with SAH. According to our knowledge, this is the first report on invasive treatment of DCI with continuous intra-arterial calcium channel blockers in awake patients without sedation.

DCI has a tremendous impact on the outcome of patients with SAH [3]. Intra-arterial application of calcium channel blockers may reverse the cerebral macrospasm [4, 12, 13]. Furthermore, it has been reported that a significant improvement of clinical outcome may be achieved even after single intra-arterial nimodipine application [13]. However, the vasodilation induced by nimodipine lasts for a short period, while severe vasospasms may last longer than 14 days. Additionally, repeated transfers to the angiography suite increase the risk for other complications. Furthermore, the typical side-effect of high-dose systemic nimodopine is arterial hypotension and hemodynamic instability. Different vasodilators have been used against CV so far, Kerz et al. compared the local intra-arterial application of nimodipine with papaverine in patients with symptomatic CV and found out that papaverine has better vasodilatory effect on vessels but without significant difference on capillary blood flow and patients' outcome at discharge [14]. In contrary to our study, local single intra-arterial application of nimodipine or papaverine was used. Negative effects of papaverine were reported by some authors [15]. Nevertheless, the role of papaverine as well as for milrinone as a treatment agent for CV and DCI remains unclear [10, 16]. Other endovascular methods offered in patients with refractory CV are balloon angioplasty and temporary deployment of retrievable intracranial stents [17–21]. However, they both require superselective catheterization of spastic small-caliber intracranial proximal arteries, which could easily cause vessel dissection and perforation and provide only treatment of proximal intracranial vasospasm. Besides, it is not clear yet, whether treating angiographic proximal vasospasm has an effect on distal vasospasm or total outcome. Studies showed that nimodipine could be effective even without causing angiographically proven regression of vasospasm, and delayed infarcts following SAH can occur in territories without angiographic vasospasm [22–24]. Based on these facts, continuous intra-arterial nimodipine application

Table 1 Patients' and treatments' characteristics (f—female, m—male, ACOM—anterior communicating artery, ICA - internal carotid artery, MCA—medial cerebral artery, PICA—posterior inferior cerebellar artery, WEB - woven endobridge device)

Age and gender	Hunt and Hess grade	Ruptured aneurysm vessel	Length of intra-arterial nimodipine therapy (days)	Treatment of ruptured aneurysm	Neurological deficit during vasospasm phase	ΔTCD 24 h before intra-arterial nimodipine (cm/s)	ΔTCD 24–48 h after intra-arterial nimodipine (cm/s)
47, f	1	MCA left and ACIICA instead of ACI left	7	WEB device and coiling	Aphasia	+ 91	− 70
49, f	2	MCA right	15	Coiling	Hemiparesis	+ 37	− 12
56, f	3	PICA left	7	WEB device	Aphasia	+ 64	− 49
52, m	5	ACOM	6	Coiling	Hemiparesis and orientation disorder	+ 44	− 34
50, f	4	MCA right	10	Clipping	Disturbance of consciousness and hemiparesis	+ 77	− 85

has been introduced in order to improve the treatment of CV and DCI. The feasibility and effect of this method were reported in some studies [8–11, 25]. In all reports, sedation and strong supine position sometimes even with rigid neck collar were described. This regimen hinders neurological evaluation of the patients and transforms beforehand awake patients to sedated patients without effective monitoring despite all methods of invasive neuromonitoring in the ICU. Furthermore, thromboembolic or bleeding complications may be difficult to reveal early in sedated patients. We have proposed to treat compliant patients with progressive neurological deficits as a consequence of DCI and CV awake with continuous intra-arterial nimodipine therapy. In all patients, excellent results could be achieved. The new DCI-induced neurological deficit was resolved within 24 h without exception. Furthermore, no severe complication related to the intra-arterial treatment occurred. Nimodipine dose given intra-arterially in the dose up to 2 mg/h is surely related not only to higher local vasodilatory effect but also could result in higher complications and side effects. Except for arterial hypotension mentioned before, other complications such as blurred vision or dizziness and pronounced sweating were reported. We found none of these complications in our small patients' cohort. Even patients with slight orientation disturbance improved after the start of the therapy. Similarly, we found no profound bleeding or local complications of prolonged catheter position. However, surely, larger studies must confirm this experience as well as superior effect of continuous intra-arterial nimodipine effect to for instance fractionated nimodipine therapy or the application of other vasodilatory agents. Nevertheless, continuous intra-arterial nimodipine application results in less transports and unnecessary manipulation as well as in prolonged nimodipine effect which might influence macrospasm and microspasm or prevent infarction resulting from DCI. Based on the same reason, microcatheters are positioned in the osseous part of both ICAs, so that macrocirculation and microcirculation of all supratentorial arterial territories may be achieved. This segment of ICA shows less vulnerability to the endovascular catheter. Moreover, that way, superselective catheterization of small spastic intracranial vessels and potentially their catheter-related occlusion may be avoided. Excellent monitoring of neurological function and monitoring of the treatment effectiveness was achieved. Only 1 patient removed the catheter unintendedly on day 7 of treatment due to a short period

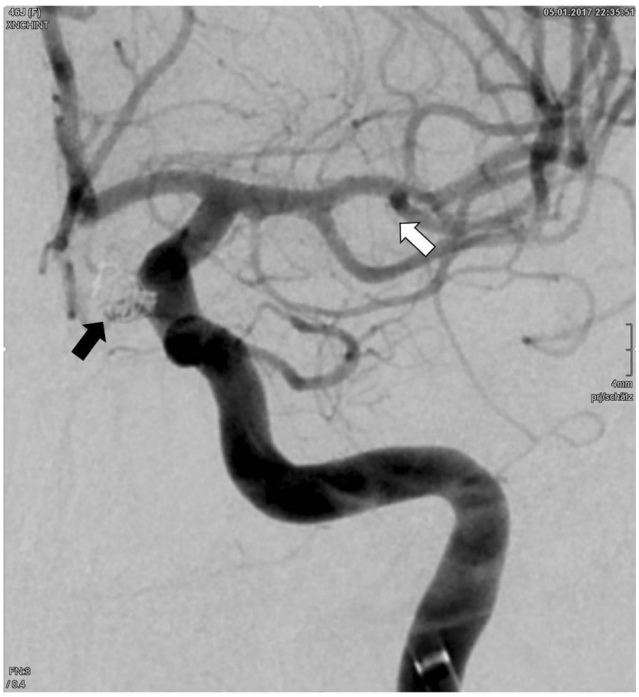

Fig. 1 Digital subtraction angiography in anteroposterior projection showing complete occlusion of the left ICA-aneurysm with coils (black arrow) and the left MCA-bifurcation-aneurysm with WEB device (white arrow). No significant vasospasm of the intracranial arteries (ICA—internal carotid artery, MCA—middle cerebral artery, WEB—Woven endoBridge embolization device)

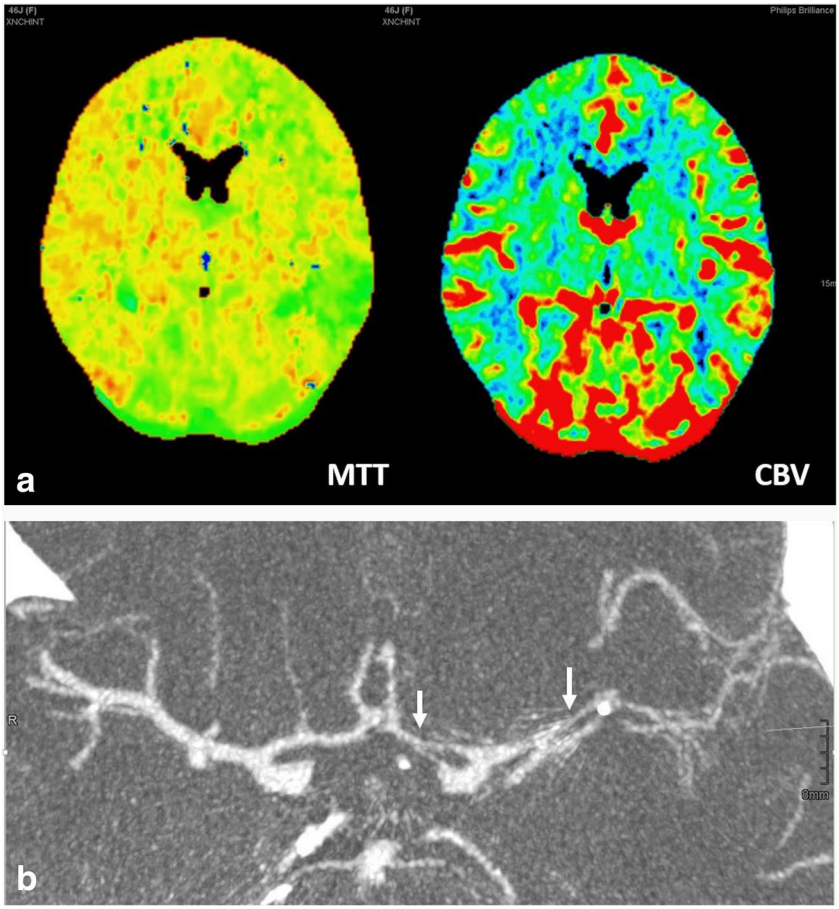

Fig. 2 **a** CT perfusion (CTP) presenting mismatch between mean transit time (MTT) and cerebral blood volume (CBV) in the left hemisphere suggesting impending infarction. **b** CT angiogram-MIP (maximum intensity projection) axial view demonstrating severe vasospasm of the left proximal anterior and medial cerebral artery (white arrows)

of disorientation and disquiet state. No further invasive CV therapy was initiated and the patient remained stable. In one case, a local thrombus was found in the femoral artery after 15 days of intra-arterial nimodipine therapy which showed regression in daily follow-up with Duplex sonography. The thrombus remained asymptomatic and since the patient was treated prophylactically with aspirin due to cardiovascular comorbidities, no additional treatment regimen was necessary.

Another important issue is that vasopressor dosage may be reduced in patients without additional sedation and ventilation, so that intra-arterial nimodipine therapy may be better tolerated. Larger studies with detailed evaluation of vasopressor dosage must clarify this statement.

CT-angiogram and perfusion as well as DSA are surely related to higher radiation exposure. MRA may be an alternative in this patient group, but it requires a careful preselection because in restless patient, motion artifacts sometimes make the examination useless. We think that MRA seldom reaches the spatial resolution of a multi-detector CT. Thus, CTA proves itself as a reliable diagnostic tool. However, routine screening with TCD and escalation of conservative treatment steps as described before prevent unnecessary radiation dose. Nevertheless, sufficient neurological monitoring and TCD may contribute to less number of additional diagnostic procedures. Similarly, if we compare single local nimodipine intra-arterial administration to continuous intra-arterial nimodipine treatment, it could be beneficial for patients even in regard to radiation exposure, since mostly repetitive local nimodipine infusions and angiograms are necessary.

The main aim of our study was to show the feasibility of this new treatment concept of CV or even DCI. Surely, based on 5 patients, it is not possible to generalize our recommendation and large prospective clinical series are necessary to confirm the effectiveness and reliability of this treatment. Even if we had no major complications, due to small number of patients, we cannot generalize our statement. Full-dose heparinization might potentially result in severe complications, even if according to our experience, it is beneficial to have the opportunity assess the clinical and neurological examination immediately, so that such a potential complication can be detected very fast. None of our patients had DCI-associated infarction on CT images at the discharge; however, no diffusion-weighed images were performed, so that detailed analysis of possible small infarction is not possible with our data. Small emboli coming from microcatheters may remain undetected even in the case of sufficient anticoagulation. However, there were no thromboembolic complications detectable according to the patients' clinical condition.

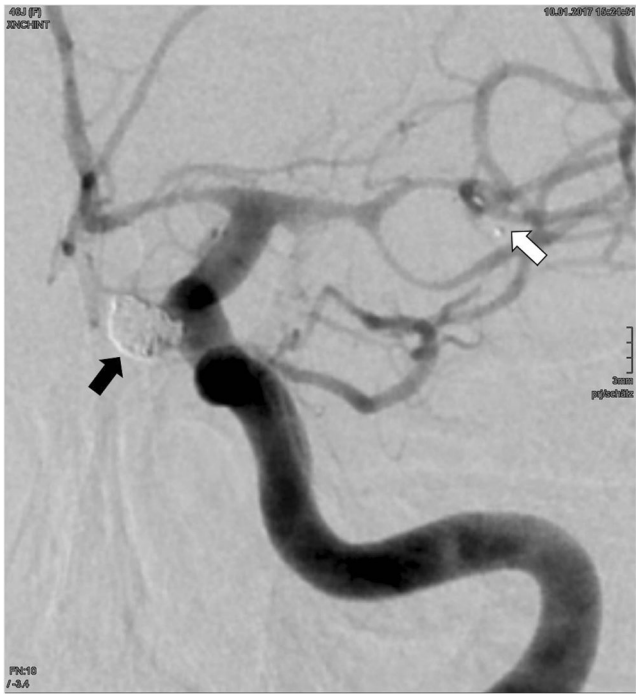

Fig. 3 Digital subtraction angiography in anteroposterior projection verified the severe vasospasm of the proximal MCA and ACA, as already seen on CT-angiogram (ACA—anterior cerebral artery, ICA - internal carotid artery, MCA—middle cerebral artery, black arrow - ICA-aneurysm occlusion with coils, white arrow - MCA-aneurysm occlusion with WEB, wowen endobridge device)

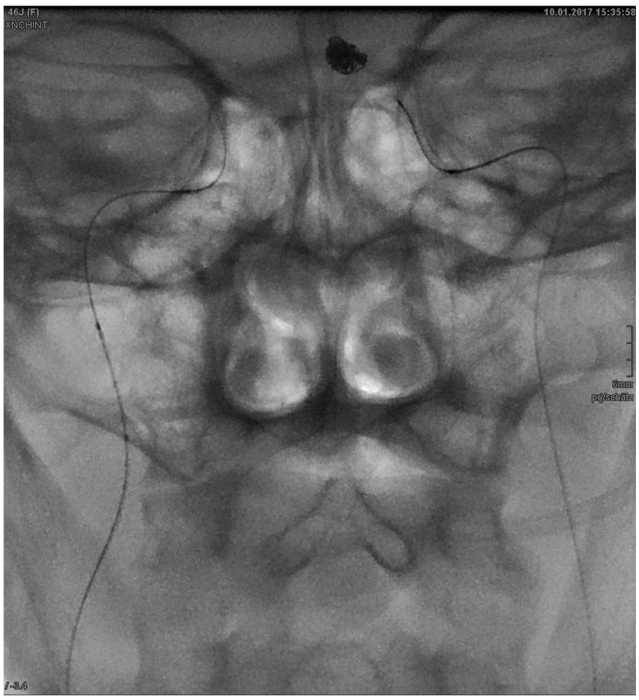

Fig. 4 Flouroscopic anteroposterior image showing intracarotid microcatheters on both side lying in the petrous portion of the ICA. Afterwards, microwires were removed and the microcatheters were connected to nimodipine infusion pump (ICA—internal carotid artery)

At the present study, we could show the effectiveness of intra-arterial calcium channel blockers' vasodilation in awake patients without the need for sedation and immobilization. This point is surely simultaneously the weak spot, since it is difficult to estimate how well the individual patient will tolerate this rather uncomfortable treatment. However, thus an excellent neurological monitoring is possible and after detailed explanation, the advantages may be discussed directly with the patient. The fast improvement of neurological deficits was impressive in all 5 cases. Even patients with orientation disturbances seem to profit from this treatment method very fast and tolerate it surprisingly well. Aggressive and non-cooperative patients are not appropriate for this treatment. However, detailed patients' characteristics that help to identify appropriate candidates for this therapy remain to be elucidated in larger studies. The pathogenesis of CV is still not completely understood. However, it seems to be a complex process not only consisting of macrovasospasm but also probably involving small vessels as well [2, 26]. For this reason, intra-arterial calcium channel blocker therapy might be much more effective and should be considered in patients with progressive neurological deficit due to DCI, even if they did not sustain a severe SAH. Those patients could benefit from continuous intra-arterial treatment, while waving of sedation allows for an excellent neuromonitoring with early detection of possible complications while eliminating its side effects.

Conclusion

We have demonstrated the feasibility and safety of the continuous intra-arterial calcium channel blockers treatment without sedation in conscious patients with DCI and CV after SAH. Excellent monitoring of the neurological function and monitoring of potential complications is possible with this method. We found no severe complications related to the awake state of patients receiving this therapy and all patients achieved excellent neurological outcome.

Acknowledgements We would like to show our gratitude to our complete ICU team for their great commitment which made a substantial contribution to this publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval nr. 168/17, Ethikkomission Ulm, retrospective study.

References

1. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Chou SN, Kelly DL, Weir BK, Crabbe RA, Lavik PJ, Rosenbloom SB,

Dorsey FC, Ingram CR, Mellits DE, Bertsch LA, Boisvert DP, Hundley MB, Johnson RK, Strom JA, Transou CR (1983) Cerebral arterial spasm—a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med 308:619–624. https://doi.org/10.1056/NEJM198303173081103

2. Sarrafzadeh AS, Vajkoczy P, Bijlenga P, Schaller K (2014) Monitoring in neurointensive care —the challenge to detect delayed cerebral ischemia in high-grade aneurysmal SAH. Front Neurol 5:134. https://doi.org/10.3389/fneur.2014.00134
3. Schweizer TA, Al-Khindi T, Macdonald RL (2012) Mini-Mental State Examination versus Montreal Cognitive Assessment: rapid assessment tools for cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. J Neurol Sci 316:137–140. https://doi.org/10.1016/j.jns.2012.01.003
4. Bashir A, Andresen M, Bartek J, Cortsen M, Eskesen V, Wagner A (2016) Intra-arterial nimodipine for cerebral vasospasm after subarachnoid haemorrhage: influence on clinical course and predictors of clinical outcome. Neuroradiol J 29:72–81. https://doi.org/10.1177/1971400915626429
5. Hockel K, Diedler J, Steiner J, Birkenhauer U, Ernemann U, Schuhmann MU (2017) Effect of intra-arterial and intravenous nimodipine therapy of cerebral vasospasm after subarachnoid hemorrhage on cerebrovascular reactivity and oxygenation. World Neurosurg 101:372–378. https://doi.org/10.1016/j.wneu.2017.02.014
6. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, Humphrey PR, Lang DA, Nelson R, Richards P (1989) Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 298:636–642. https://doi.org/10.1136/bmj.298.6674.636
7. Wolf S, Martin H, Landscheidt JF, Rodiek SO, Schürer L, Lumenta CB (2010) Continuous selective intraarterial infusion of nimodipine for therapy of refractory cerebral vasospasm. Neurocrit Care 12:346–351. https://doi.org/10.1007/s12028-009-9317-6
8. Hockel K, Diedler J, Steiner J, Birkenhauer U, Danz S, Ernemann U, Schuhmann MU (2016) Long-term, continuous intra-arterial nimodipine treatment of severe vasospasm after aneurysmal subarachnoid hemorrhage. World Neurosurg 88:104–112. https://doi.org/10.1016/j.wneu.2015.11.081
9. Mayer TE, Dichgans M, Straube A, Birnbaum T, Müller-Schunk S, Hamann GF, Schulte-Altedorneburg G (2008) Continuous intra-arterial nimodipine for the treatment of cerebral vasospasm. Cardiovasc Intervent Radiol 31:1200–1204. https://doi.org/10.1007/s00270-008-9346-0
10. Musahl C, Henkes H, Vajda Z, Coburger J, Hopf N (2011) Continuous local intra-arterial nimodipine administration in severe symptomatic vasospasm after subarachnoid hemorrhage. Neurosurgery 68:1541–1547– discussion 1547. https://doi.org/10.1227/NEU.0b013e31820edd46
11. Ott S, Jedlicka S, Wolf S, Peter M, Pudenz C, Merker P, Schürer L, Lumenta CB (2014) Continuous selective intra-arterial application of nimodipine in refractory cerebral vasospasm due to aneurysmal subarachnoid hemorrhage. Biomed Res Int 2014:970741–970711. https://doi.org/10.1155/2014/970741
12. Biondi A, Ricciardi GK, Puybasset L, Abdennour L, Longo M, Chiras J, Van Effenterre R (2004) Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: preliminary results. Am J Neuroradiol 25:1067–1076
13. Hanggi D, Turowski B, Beseoglu K, Yong M, Steiger HJ (2008) Intra-arterial nimodipine for severe cerebral vasospasm after aneurysmal subarachnoid hemorrhage: influence on clinical course and cerebral perfusion. Am J Neuroradiol 29:1053–1060. https://doi.org/10.3174/ajnr.A1005
14. Kerz T, Boor S, Beyer C, Welschehold S, Schuessler A, Oertel J (2012) Effect of intraarterial papaverine or nimodipine on vessel diameter in patients with cerebral vasospasm after subarachnoid hemorrhage. Br J Neurosurg 26:517–524. https://doi.org/10.3109/02688697.2011.650737
15. Miller JA, Cross DT, Moran CJ, Dacey RG, McFarland JG, Diringer MN (1995) Severe thrombocytopenia following intraarterial papaverine administration for treatment of vasospasm. J Neurosurg 83:435–437. https://doi.org/10.3171/jns.1995.83.3.0435
16. Shankar JJS, Santos dos MP, Deus-Silva L, Lum C (2011) Angiographic evaluation of the effect of intra-arterial milrinone therapy in patients with vasospasm from aneurysmal subarachnoid hemorrhage. Neuroradiology 53:123–128. https://doi.org/10.1007/s00234-010-0720-7
17. Bhogal P, Loh Y, Brouwer P, Andersson T, Söderman M (2017) Treatment of cerebral vasospasm with self-expandable retrievable stents: proof of concept. J Neurointerv Surg 9:52–59. https://doi.org/10.1136/neurintsurg-2016-012546
18. Chalouhi N, Tjoumakaris S, Thakkar V, Theofanis T, Hammer C, Hasan D, Starke RM, Wu C, Gonzalez LF, Rosenwasser R, Jabbour P (2014) Endovascular management of cerebral vasospasm following aneurysm rupture: outcomes and predictors in 116 patients. Clin Neurol Neurosurg 118:26–31. https://doi.org/10.1016/j.clineuro.2013.12.012
19. Kerz T, Boor S, Ulrich A, Beyer C, Hechtner M, Mueller-Forell W (2016) Endovascular therapy for vasospasm after aneurysmatic subarachnoid hemorrhage. Br J Neurosurg 30:549–553. https://doi.org/10.3109/02688697.2016.1173193
20. Khatri R, Memon MZ, Zacharatos H, Taqui AM, Qureshi MH, Vazquez G, Suri MFK, Rodriguez GJ, Tummala RP, Ezzeddine MA, Qureshi AI (2011) Impact of percutaneous transluminal angioplasty for treatment of cerebral vasospasm on subarachnoid hemorrhage patient outcomes. Neurocrit Care 15:28–33. https://doi.org/10.1007/s12028-010-9499-y
21. Patel AS, Griessenauer CJ, Gupta R, Adeeb N, Foreman PM, Shallwani H, Moore JM, Harrigan MR, Siddiqui AH, Ogilvy CS, Thomas AJ (2017) Safety and efficacy of noncompliant balloon angioplasty for the treatment of subarachnoid hemorrhage-induced vasospasm: a multicenter study. World Neurosurg 98:189–197. https://doi.org/10.1016/j.wneu.2016.10.064
22. Brown RJ, Kumar A, Dhar R, Sampson TR, Diringer MN (2013) The relationship between delayed infarcts and angiographic vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurgery 72:702–707– discussion 707–8. https://doi.org/10.1227/NEU.0b013e318285c3db
23. Dhar R, Diringer MN (2015) Relationship between angiographic vasospasm, cerebral blood flow, and cerebral infarction after subarachnoid hemorrhage. Acta Neurochir Suppl 120:161–165. https://doi.org/10.1007/978-3-319-04981-6_27
24. Laskowitz DT, Kolls BJ (2010) Neuroprotection in subarachnoid hemorrhage. Stroke 41:S79–S84. https://doi.org/10.1161/STROKEAHA.110.595090
25. Bele S, Proescholdt MA, Hochreiter A, Schuierer G, Scheitzach J, Wendl C, Kieninger M, Schneiker A, Bründl E, Schödel P, Schebesch KM, Brawanski A (2015) Continuous intra-arterial nimodipine infusion in patients with severe refractory cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a feasibility study and outcome results. Acta Neurochir 157:2041–2050. https://doi.org/10.1007/s00701-015-2597-z
26. Østergaard L, Aamand R, Karabegovic S, Tietze A, Blicher JU, Mikkelsen IK, Iversen NK, Secher N, Engedal TS, Anzabi M, Jimenez EG, Cai C, Koch KU, Naess-Schmidt ET, Obel A, Juul N, Rasmussen M, Sørensen JCH (2013) The role of the microcirculation in delayed cerebral ischemia and chronic degenerative changes after subarachnoid hemorrhage. J Cereb Blood Flow Metab 33:1825–1837. https://doi.org/10.1038/jcbfm.2013.173