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Intraarterial nimodipine versus induced hypertension for delayed cerebral ischemia – a modified treatment protocol

Miriam Weiss, MD[1,2], **Walid Albanna, MD**[1], **Catharina Conzen-Dilger, MD**[1], **Nick Kastenholz, cand. med.**[1], **Katharina Seyfried, MD**[1], **Hani Ridwan, MD**[3], **Martin Wiesmann, MD**[3], **Michael Veldeman, MD, PhD**[1], **Tobias Philip Schmidt, MD, MHBA**[1], **Murad Megjhani, PhD**[4,5], **Henna Schulze-Steinen, MD**[8], **Hans Clusmann, MD**[1], **Marcel Johannes Hermanus Aries, MD, PhD**[6,7], **Soojin Park, MD, FAHA, FNCS**[4,5,9], **Gerrit Alexander Schubert, MD**[1,2]

[1]Department of Neurosurgery, RWTH Aachen University, Aachen, Germany

[2]Department of Neurosurgery, Kantonsspital Aarau, Switzerland

[3]Department of Diagnostic and Interventional Neuroradiology, RWTH Aachen University, Aachen, Germany

[4]Program for Hospital and Intensive Care Informatics, Department of Neurology, Columbia University Irving Medical Center, New York, USA

[5]NewYork Presbyterian Hospital, Columbia University Irving Medical Center, New York, USA

[6]Department of Intensive Care, Maastricht University Medical Center, Maastricht University, Maastricht, The Netherlands

[7]School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Center, Maastricht, The Netherlands

[8]Department of Intensive Care Medicine and Perioperative Care, RWTH Aachen University, Aachen, Germany

[9]Department of Biomedical Informatics, Columbia University, New York, USA

Abstract

Background: Rescue treatment for delayed cerebral ischemia (DCI) after subarachnoid hemorrhage can include induced hypertension (iHTN) and, in refractory cases, endovascular approaches, of which selective, continuous intraarterial nimodipine (IAN) is one variant. The combination of iHTN and IAN can dramatically increase vasopressor demand. In case of unsustainable doses, iHTN is often prioritized over IAN. However, evidence in this regard is largely lacking. We investigated the effects of a classical (iHTN+IAN) and modified (IAN_{only}) treatment protocol for refractory DCI in an observational study.

Methods: Rescue treatment for DCI was initiated with iHTN (target >180mmHg systolic) and escalated to IAN in refractory cases. Until 07/2018, both iHTN and IAN were offered in cases refractory to iHTN alone. After protocol modification, iHTN target was preemptively lowered

Corresponding author: Miriam Weiss, Department of Neurosurgery, RWTH Aachen University, Pauwelsstrasse 30, 52074 Aachen, Germany, miriam_weiss@icloud.com.

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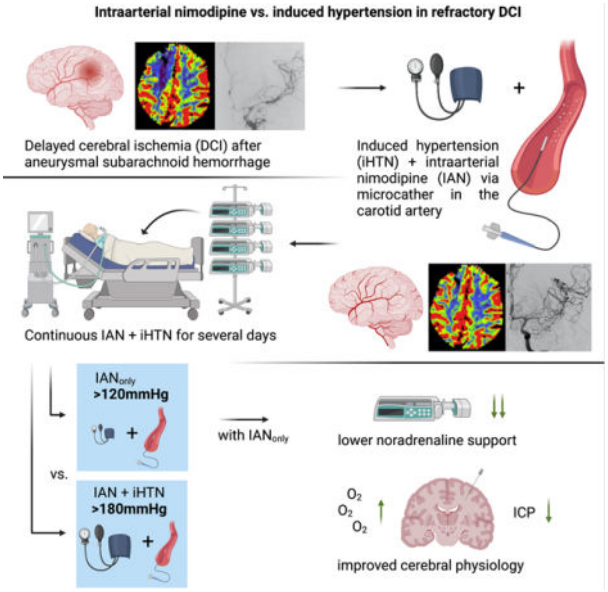
to >120mmHg when IAN was initiated (IAN_{only}). Primary outcome was noradrenaline demand. Secondary outcomes included noradrenaline-associated complications, brain tissue oxygenation ($p_{ti}O_2$), DCI-related infarction and favorable 6-month outcome (Glasgow Outcome Scale 4–5).

Results: N=29 and n=20 patients were treated according to the classical and modified protocol, respectively. Protocol modification resulted in a significant reduction of noradrenaline demand (iHTN+IAN 0.70±0.54μg/kg/min, IAN_{only} 0.26±0.20μg/kg/min, p<0.0001) and minor complications (15.0% versus 48.3%, unadjusted OR 0.19 (95% CI 0.05–0.79), p<0.05) with comparable rates of major complications (20.0% versus 20.7%, OR 0.96 (0.23–3.95), p=0.95). Incidence of DCI-related infarction (45.0% versus 41.1%, OR 1.16 (0.37–3.66), p=0.80) and favorable clinical outcome (55.6% versus 40.0%, OR 1.88 (0.55–6.39), p=0.32) were similar. $P_{ti}O_2$ was significantly higher with IAN_{only} (26.6±12.8mmHg, 39.6±15.4mmHg, p<0.01).

Conclusions: Assuming the potential of iHTN to be exhausted in case of refractory hypoperfusion, additional IAN may serve as a last-resort measure to bridge hypoperfusion in the DCI phase. With close monitoring, preemptive lowering of pressure target after induction of IAN may be a safe alternative to alleviate total noradrenaline load and potentially reduce complication rate.

Graphical Abstract



Introduction

Delayed cerebral ischemia (DCI) is one of the known key contributors to cognitive impairment after aneurysmal subarachnoid hemorrhage[1]. The currently recommended treatment modalities for DCI are largely aimed at maximizing supply to underserved territories, regardless of the exact underlying pathomechanism(s). If DCI occurs, vasopressor-induced hypertension (iHTN) is a common, albeit critically debated first-line approach to improve perfusion[2]. Further escalation in case of refractory DCI may ultimately include local application of vasodilators as second-line therapy. However, there is still a lack

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of robust evidence regarding the guidance of rescue treatment for DCI, resulting in highly heterogenous treatment algorithms[3,4]. Controlled trials for endovascular rescue treatment are not available and unlikely to be performed due to the ethical concern of withholding treatment at this critical point[5]. The latest international guidelines generally recommend iHTN as primary rescue treatment and intraarterial vasodilation as adjunct with weaker recommendation but are unable to provide clear directive due to the paucity of evidence[5–8]. Short-term, repetitive intraarterial spasmolysis in the angiography suite is a common form of endovascular rescue treatment[3]. Leaving the intraarterial catheter(s) in place and continuing vasodilation in the intensive care unit is a less frequently practiced method, accompanied by a separate risk profile but with the opportunity to bridge the oftentimes prolonged DCI phase[9,10]. Centers implementing continuous endovascular rescue treatment may frequently observe an inherent conflict of mechanisms when adding intraarterial vasodilation on top of iHTN. Secondary systemic distribution of a locally applied vasodilator often increases vasopressor demand to counteract this effect peripherally[11]. Escalation of vasopressor support may facilitate dangerous complications up to cardiopulmonary exhaustion and multi-organ failure due to impairment of microcirculatory perfusion, requiring reduction of rescue treatment to curb vasopressor demand[12]. A balance must be found between the risk of cerebral infarction and a critical compromise of peripheral microcirculation. There is, however, currently no evidence on the prioritization of iHTN over intraarterial vasodilation, nor on the safety and efficacy of measures to reduce vasopressor demand in either scenario.

We have previously documented our standard operating procedure with continuous intraarterial nimodipine (IAN) in case of DCI refractory to iHTN and found promising effects on cerebral hypoxia and disturbed local metabolism[9,13]. Nevertheless, we also encountered critical vasopressor increases which classically triggered reduction of IAN while iHTN was maintained. In search for an alternative algorithm with lower vasopressor demand but non-inferior efficacy, we hypothesized that the effect of iHTN on DCI may be exhausted in cases with refractory hypoperfusion. We modified our treatment protocol accordingly, henceforth lowering our pressure-target preemptively when IAN was initiated after failure of iHTN. The aim of this prospective observational study was to compare our classical (iHTN+IAN) and modified (IAN_{only}) treatment protocols in patients refractory to iHTN alone, with the hypothesis that protocol modification would lead to lower vasopressor demand without a compromise in rescue treatment efficacy.

Methods

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

Patient cohort

Data of patients ≥18 years who were treated at our institution for verified aSAH between January 2014 to December 2020 were collected into a prospective databank. Patients with DCI deemed refractory to iHTN were included into this observational study. Written, informed consent for databank inclusion and data analysis was obtained by a legal

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representative if capacity for informed decision making was absent. Approval was granted by a local ethics committee (EK062/14). Reporting follows the STROBE criteria[14].

Classical and modified DCI treatment protocols

Figure 1 details our treatment algorithm with a classical protocol (iHTN+IAN) followed by protocol modification in 07/2018 (IAN_{only}). All aSAH patients were cared for in an intensive care unit specialized on care of neurosurgical patients after securing the ruptured aneurysm. Fluid balance is targeted at −500 to 0ml daily and further fluid management is aligned with the KDIGO guideline[15]. All patients received oral nimodipine prophylaxis with 360mg/day unless contraindicated. Awake patients were monitored for DCI clinically, while unconscious and/or analgosedated patients or those at high risk for DCI (Hunt and Hess grade ≥3, or grade 1–2 with modified Fisher grade ≥3, unless the hemorrhage is deemed fatal) received invasive neuromonitoring probes consisting of a combined $p_{ti}O_2$/ICP-probe (Neurovent PTO, Raumedic, Helmbrechts, Germany) and adjacent cerebral microdialysis (71 High Cut-Off Brain Microdialysis Catheter, μdialysis, Stockholm, Sweden). Probes were placed into the watershed area between anterior and middle cerebral artery territories on the side of the offending aneurysm, or in the non-dominant hemisphere for midline aneurysms. Transcranial doppler sonography was used on an as needed basis.

In awake patients, DCI was diagnosed according to the definition by Vergouwen et al.[16]. If clinical examination was not available, functional deterioration as observed by invasive neuromonitoring (individual worsening of $p_{ti}O_2$ or lactate/pyruvate ratio) was used to trigger CT perfusion, in which case territorial or watershed perfusion deficit (time to drain >10s, mean transit time >6.7s) was included to also diagnose DCI. The term “DCI” therefore refers to either the first clinical deterioration or to CT perfusion deficit in this cohort. Of note, during IAN, where patients are analgosedated (see below), only repeated CT perfusion scans can indicate if DCI is still ongoing. Infarction on native CT imaging is termed DCI related infarction (if deemed unrelated to embolic infarction).

After DCI diagnosis, iHTN served as first-line treatment with systolic blood pressure >180mmHg by intravenous noradrenaline infusion in both protocols. If clinical deficit or hypoperfusion on CT perfusion persisted or aggravated under iHTN, digital subtraction angiography was conducted. Moderate vasoconstriction and perfusion delay of contrast agent were criteria to consider additional, continuous intraarterial nimodipine application (IAN). For this purpose, microcatheters were placed into one or both internal carotid arteries and/or one vertebral artery depending on the affected regions. Infusion amounted to a maximum cumulative dose of 2mg/h. IAN was accompanied by deep analgosedation (Riker Sedation Agitation Scale 1–2 (unarousable or very sedated) by infusion of propofol, midazolam, ketamine and/or clonidine together with sufentanil), inhibition of platelet-aggregation by tirofiban (Aggrastat®, Correvio, Heathrow, United Kingdom), and minimal patient handling.

Under the classical protocol, iHTN was maintained with a pressure target >180mmHg after initiation of IAN (iHTN+IAN). In case of critical escalation of noradrenaline demand (>0.5μg/kg/min), a risk-benefit assessment was made by the treating team whether to maintain or reduce rescue treatment. Without present or anticipated noradrenaline-related

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complications and persistent indication for iHTN and IAN in CT perfusion, treatment was continued despite noradrenaline dose >0.5μg/kg/min. Otherwise, IAN dose was reduced to 0.5–1mg/h or terminated completely while pressure target remained >180mmHg. If this did not lower vasopressor demand sufficiently, pressure target was also lowered (up to a safety limit >120mmHg). After protocol modification, rescue treatment was escalated comparably (iHTN >180mmHg as first-line, IAN as second line), but the pressure target was preemptively lowered to >120mmHg systolic blood pressure with the initiation of IAN. To ensure safety of this modification to our approach, CT perfusion was performed immediately after the induction of IAN under normotensive blood pressure regime to document sufficient reversal of hypoperfusion. Reduction of rescue treatment was evaluated analogously to the classical protocol (risk-benefit assessment with noradrenaline >0.5μg/kg/min) and, if noradrenaline-related complications (see below) were present or anticipated, IAN dosage was reduced in a step-wise fashion. Rescue treatment was maintained until resolution of DCI as shown by neuromonitoring and CT perfusion studies, overall condition of the patient and timing within DCI phase. In case of microcatheter thrombosis, the catheter was removed in the angiography suite and timely CT perfusion was conducted. If perfusion re-deterioration was observed on CT perfusion imaging following thrombosis or elective nimodipine dose reduction, microcatheters were replaced again and/or nimodipine treatment was re-escalated. In patients with iHTN+IAN, the pressure target was also re-escalated >180mmHg with microcatheter replacement, while it remained >120mmHg in patients with IAN_{only}.

Outcome parameters

Baseline demographic parameters were recorded, as were details of the clinical course and neuromonitoring data. The primary outcome parameter was the mean noradrenaline demand for the whole duration of combined iHTN+IAN treatment or IAN_{only}, respectively. Breaks between IAN applications >24hours were excluded from mean value calculations. Secondary outcome parameters were focused on the safety of noradrenaline application and the efficacy of cerebral rescue treatment.

Safety We recorded the number of additional treatment de-escalations to curb noradrenaline demand (reduction of pressure target or IAN dose, according to each protocol). We compared the frequency of side effects that may be caused or aggravated by prolonged, high noradrenaline infusion. Side effects were stratified into minor complications with optional treatment reduction (peripheral limb malperfusion visible as cooled, blanched or marbled extremities; new cardiac arrhythmia) and major complications with obligatory interruption of rescue treatment (new cardiac insufficiency diagnosed by transthoracic echocardiography, cardiogenic shock or myocardial infarction with or without ST-elevation; paralytic ileus or diffuse ischemic gastrointestinal injury; secondary sclerosing cholangitis in critically ill patients). The number of CT perfusion scans during IAN (including for diagnosis of DCI) were documented per group. Complications associated with indwelling microcatheters were also documented (thrombosed microcatheter or visible thrombi surrounding the catheter in CT angiography or digital subtraction angiography, necessary re-angiography with catheter replacement, thromboembolic cerebral infarction or venous or arterial thromboembolism diagnosed during IAN or up to one week after catheter removal).

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Efficacy To evaluate the efficacy of cerebral rescue treatment, we calculated mean brain tissue oxygenation ($p_{ti}O_2$) and ICP during treatment, recorded the number of patients with ≥1 necessary treatment re-escalation (with or without previous reduction of pressure target or IAN dose, any time CT perfusion indicated that the current strategy was insufficient, according to each protocol), the occurrence of DCI related cerebral infarction (consistent with current or previously hypoperfused territory, absence of thrombi)[16], clinical outcome 6 months after discharge with Glasgow Outcome Scale 4–5 defined as favorable outcome, as well as duration of treatment and hospitalization.

Statistical analysis

Statistical analyses were conducted with IBM SPSS Statistics 26 (SPSS Inc., Chicago, IL, USA). Graphical elements were created using GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, USA). Continuous parameters are shown as mean ± standard deviation, discrete variables as n (percentage). Continuous data were tested for normality distribution with the Kolmogorow-Smirnov normality test. Unpaired t-test or Mann-Whitney U test assessed differences between groups, as appropriate. Fisher's exact test was used for comparisons of discrete demographic variables. Binary outcome parameters were compared in a univariate logistic regression analysis and an unadjusted odds ratio (OR) with 95% confidence interval (CI) was calculated. Two-sided *p*-values <0.05 were considered statistically significant. Missing data were not imputed.

Results

Out of n=243 patients with SAH treated at our institution in the respective time frame, n=49 (20.2%) developed DCI refractory to iHTN. 29 patients were treated with the iHTN+IAN and 20 with IAN_{only}. Baseline demographic and bleeding characteristics were comparable between both groups (Table 1). IHTN was initiated 5.4±2.7 and 8.1±3.4 days after hemorrhage (p<0.01), followed by IAN 2.6±2.7 and 1.8±2.3 days afterwards (p=0.36) in patients with iHTN+IAN and IAN_{only}, respectively. N=10 (34.5%) patients with iHTN+IAN had one repeat endovascular intervention with microcatheter replacement (after elective removal or thrombosed catheter), n=1 (3.5%) had three repeat interventions. Of patients with IAN_{only}, n=4 (20.0%) had one and n=1 (5.0%) had three repeat intervention. 21 patients with iHTN+IAN (72.4%) and 11 patients with IAN_{only} (55.0%) had a $p_{ti}O_2$/ICP-probe. Nimodipine dose during total treatment duration was similar (iHTN+IAN 19.0±7.7μg/kg/h, IAN_{only} 19.8±7.7μg/kg/h, p=0.61), but systolic blood pressure was significantly lower with IAN_{only} (iHTN+IAN 185±15.0mmHg, IAN_{only} 154.8±15.0mmHg, p<0.0001).

Safety

Noradrenaline demand was significantly lower in patients with IAN_{only} (iHTN+IAN 0.70±0.54μg/kg/min, IAN_{only} 0.26±0.20μg/kg/min, p<0.0001) (Figure 2). The proportion of patients developing minor complications was lower with IAN_{only} (iHTN+IAN n=14 (48.3%), IAN_{only} n=3 (15.0%), OR 0.19 (95% CI 0.05–0.79), p<0.05), while the frequency of major complications was unchanged (iHTN+IAN n=6 (20.7%), IAN_{only} n=4 (20.0%), OR 0.96 (95% CI 0.23–3.95), p=0.95) (Table 2). The proportion of patients with any further coerced treatment de-escalations due to high vasopressor demand or complications

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was also comparable (iHTN+IAN n=15 (51.7%), IAN_{only} n=7 (35.0%), OR 0.50 (95% CI 0.16–1.62), p=0.25) but the noradrenaline dose at which treatment was de-escalated was significantly lower after protocol modification (iHTN+IAN 1.31±0.63μg/kg/min, IAN_{only} 0.73±0.24μg/kg/min, p<0.01). Patients with iHTN+IAN received a mean number of 4.7±2.5 CT perfusion scans during IAN, while patients with IAN_{only} received 6.1±3.3 scans (p=0.12). Complications ascribable to intraarterial microcatheters were not different between groups (thrombosed microcatheter or thrombi surrounding the catheter in imaging iHTN+IAN n=6 (20.7%), IAN_{only} n=5 (25.0%), OR 1.28 (95% CI 0.33–4.95), p=0.72; replacement of microcatheter due to previous catheter thrombosis iHTN+IAN n=5 (17.2%), IAN_{only} n=3 (15.0%), OR 0.85 (95% CI 0.18–4.03), p=0.84; thromboembolic cerebral infarction iHTN+IAN n=3 (10.3%), IAN_{only} n=1 (5.0%), OR 0.46 (95% CI 0.04–4.73), p=0.51; venous or arterial thromboembolism iHTN+IAN n=3 (10.3%), IAN_{only} n=6 (30.0%), OR 3.71 (95% CI 0.80–17.16), p=0.09).

Efficacy

In patients with IAN_{only}, mean $p_{ti}O_2$ during the total treatment duration was significantly higher (iHTN+IAN 26.6±15.3mmHg, IAN_{only} 39.6±15.4mmHg, p<0.01) (Figure 3A). ICP was lower with IAN_{only} (iHTN+IAN 12.0±5.0mmHg, IAN_{only} 8.1±2.3mmHg, p<0.01) (Figure 3B). Re-escalations of treatment (re-increase of nimodipine dose or pressure target) (iHTN+IAN n=17 (58.6%), IAN_{only} n=13 (65.0%), OR 1.31 (95% CI 0.40–4.26), p=0.65) were observed in a comparable number of cases. With IAN_{only}, the total duration of IAN was longer (iHTN+IAN 7.6±4.7 days, IAN_{only} 11.5±6.2 days, p<0.05). Hospitalization time was similar (iHTN+IAN 38.8±17.5 days, IAN_{only} 42.7±10.0 days, p=0.38). The overall occurrence of DCI related infarction was comparable (iHTN+IAN n=12 (41.1%), IAN_{only} n=9 (45.0%), OR 1.16 (95% CI 0.37–3.66), p=0.80) as was clinical outcome 6 months after discharge with favorable Glasgow Outcome Scale in n=10 (40.0%) patients with iHTN+IAN and in n=10 (55.6%) patients with IAN_{only} (OR 1.88 (95% CI 0.55–6.39), p=0.32). Four patients with IHTN+IAN and two patients with IAN_{only} were lost to follow-up.

Discussion

We recently changed our treatment algorithm in the context of refractory DCI and shifted emphasis of treatment towards intraarterial vasodilation with preemptive lowering of target pressure towards normotension. Protocol modification proved effective in terms of our primary outcome as mean noradrenaline demand was significantly reduced. This is particularly important as many patients in both groups exceeded our internal noradrenaline threshold of >0.5μg/kg/min, beyond which treatment reduction is discussed in a risk-benefit analysis of rescue treatment versus potential complications. Without present or anticipated complications, rescue treatment was oftentimes prioritized over absolute noradrenaline demand. Minor complications of noradrenaline treatment were less frequent but severe complications may nevertheless occur. In a stable situation with IAN and without infections, iHTN target may be a driving factor of noradrenaline demand and reduce minor complications if noradrenaline demand is consistently low (IAN_{only}) rather than moderately elevated (iHTN+IAN). Major complications occurred with severe escalations of noradrenaline demand. It was our observation that severe escalations of vasopressor

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demand were triggered by concomitant infections, common in the critical care setting and unrelated to iHTN target, which may account for the lack of difference between both groups. Early, rigorous treatment of infection may therefore be equally important to avoid major complications as reducing baseline vasopressor demand by protocol adjustment.

Protocol modification was also associated with a longer total duration of IAN, and thus prolonged need for platelet aggregation inhibition, analgosedation and minimal handling. Continuous intraarterial spasmolysis in awake patients has been reported in few selected cases with focal neurological deficit only, while the majority of patients is either not eligible for wake-up trial or has a high risk of failure due to lack of orientation and manageability with an intraarterial microcatheter in place[17]. Thromboembolic complications were overall comparable but extracranial thromboses were more frequent with the new protocol occurring in about a third of cases, although this effect was not statistically significant. Of note, platelet aggregation inhibition may benefit cerebral perfusion on top of nimodipine's vasodilating effect by preventing and/or treating cerebral microthrombosis as part of the presumed pathophysiology of DCI[18]. These potentially synergistic effects cannot be separated in our cohort but platelet aggregation inhibition has been emerging in recent years from a by-product of endovascular catheterization to being investigated as a separate form of DCI treatment[19].

We also evaluated the efficacy of rescue treatment with IAN_{only} as compared to iHTN+IAN and expected no difference. Respective variables confirmed similar treatment outcomes, including comparable rates of DCI related infarction and clinical outcome. Interestingly, intracranial pressure was lower and brain tissue oxygenation was significantly higher in patients with IAN_{only}, suggesting that lower doses of noradrenaline and/or less aggressive hypertension may even have a beneficial effect on cerebral physiology. ICP is typically stabilized by cerebral autoregulation and should be largely unaffected by fluctuations in blood pressure. Higher concentrations of noradrenaline in the iHTN+IAN group could even be hypothesized to lead to lower ICP by noradrenaline-mediated vasoconstriction (analogously to the effects of ICP treatment by hyperventilation). However, impairment of autoregulation is considered part of the pathophysiology of DCI and may additionally be severely disturbed by intraarterial nimodipine infusion as shown by Hockel et al.[20]. Assuming that autoregulation could be similarly disturbed in this severely compromised patient cohort during nimodipine infusion, ICP may react more passively to blood pressure variations[21]. This may in turn lead to lower ICP with much lower blood pressure in patients treated with IAN_{only} (ICP increase with high blood pressure during disturbed autoregulation > ICP decrease through noradrenaline).

Higher brain tissue oxygen values may result from improved oxygen delivery. Noradrenaline activates $\alpha-1$ adrenergic receptors on blood vessels with vasoconstriction and blood pressure increase as part of the flight-reflex. Although the role of noradrenaline in cerebral $\alpha-1$ activation is controversial, the current understanding is that this activation is much less pronounced in cerebral blood vessels under normal circumstances, preventing unwanted cerebral vasoconstriction. There is mounting evidence that the usually inert cerebral $\alpha-1$ response to noradrenaline may be altered during aSAH with higher catecholamine sensitivity after brain hemorrhage, hypertension or hypoxia[22]. At the same time, it has been shown

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that α−1 mediated vasoconstriction of cerebral arterioles is stronger with increasing doses of noradrenaline and additionally altered with analgosedation[23,24]. While this reflex may avoid hyperperfusion during episodes of extreme adrenergic activation, it could counteract the intended effects of hemodynamic augmentation with vasopressors. Conversely, high noradrenaline doses may also impede nimodipine-mediated vasodilation. Intracellular Ca^{2+} is released as part of the activated α−1 cascade to initiate constriction of the smooth muscle cell layer in response to noradrenaline, counteracting nimodipine as a Ca^{2+}-channel blocker in the same cellular compartment. Thus, by reducing pressure target and noradrenaline doses with IAN_{only}, $p_{ti}O_2$ may increase through less pronounced adrenergic activation despite lower cerebral perfusion pressure. In our cohort with the modified protocol, this did not translate into a significant clinical benefit as measured by GOS after 6 months, although any effect would likely not be detectable due to the limited sample size; more subtle advantages, however, may only become apparent at a later follow-up or with detailed neuropsychological testing, as these deficits are frequently reported in SAH patients but are not regularly assessed.

The need to advance rescue treatment for DCI is pressing as convincing evidence for treatment escalation beyond iHTN is still lacking, resulting in highly divergent treatment algorithms for DCI, guided by clinical experience and opinion[3]; our own treatment protocol and modification are no exemption to this. At most, there is consensus to reduce oral nimodipine during episodes of hypotension[5]. Excessive increase of vasopressor requirements is a frequent observation with continuous intraarterial vasodilation and has triggered the development of alternative delivery strategies, including local application of vasodilating agents into the cerebrospinal fluid system[10]. Examples are nimodipine microparticles delivered via external ventricular drain (NEWTON trial) or nicardipine pellets placed onto brain cortex surgically (NicaPlant) but superiority of such approaches could not be demonstrated recently[25,26]. Prophylactic alternatives to oral nimodipine such as cilostazol may have similar effects on cerebral infarction but do not prevent the necessity for effective rescue strategies as measures of last resort[27]. A variety of intravenous or intraarterial, short- or longer-term applications of several vasodilators (e.g. nimodipine, nicardipine, milrinone, verapamil) is being utilized as rescue treatment without dominant evidence for any one approach that may justify introducing it as global standard treatment. Intravenous approaches lack the risk of catheterization but supposedly reach lower local concentrations of the vasodilating agent with a similar risk of hypotension and increased vasopressor demand[28]. Whether vasopressor support is lower with short-term intraarterial spasmolysis is plausible but has not been investigated so far. However, short-term spasmolysis may have to be repeated more frequently with the risk of infarction in between procedures and additional interventional risk[29]. With an established protocol and effective interdisciplinary collaboration, we believe that continuous intraarterial vasodilation with nimodipine is appropriate as treatment for refractory DCI due to the oftentimes prolonged disease course. Recognizing the limitations and risk profile, our study supports that iHTN can be reduced to a safety limit with nimodipine infusion with beneficial effects on vasopressor demand and cerebral physiology.

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Limitations

The sample size, lack of neuromonitoring data in some patients and of a randomization protocol are the main limitations of our study. The study is not powered to detect differences in clinical outcome. Our diagnostic and treatment protocol was created in this form in 2014, with the introduction of invasive neuromonitoring and an extended DCI definition (CT perfusion deficit additional to clinical deterioration). All patients were treated according to this protocol, but the cohort with iHTN+IAN was collected before the IAN_{only} cohort. We could not identify reasons for the later time point of DCI diagnosis in patients with IAN_{only}, particularly contrary to the trend of earlier DCI diagnosis with invasive neuromonitoring in our center[30]. We are not aware of other diagnostic or treatment changes during this time, but further confounders cannot be completely excluded.

Conclusion

Aggressive rescue treatment for DCI with iHTN and IAN may require excessive vasopressor support. Preemptive lowering of pressure target after induction of IAN can dramatically reduce vasopressor requirements and improve cerebral oxygenation while lowering intracranial pressure. Our protocol modification may serve as incentive for centers active in endovascular rescue treatment to review options of protocol change to reduce vasopressor dosages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Disclosures

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Non-Standard Abbreviations and Acronyms:

aSAH	aneurysmal subarachnoid hemorrhage
DCI	delayed cerebral ischemia
IAN	continuous intraarterial nimodipine
ICP	intracranial pressure
iHTN	induced hypertension
$p_{ti}O_2$	brain tissue oxygenation

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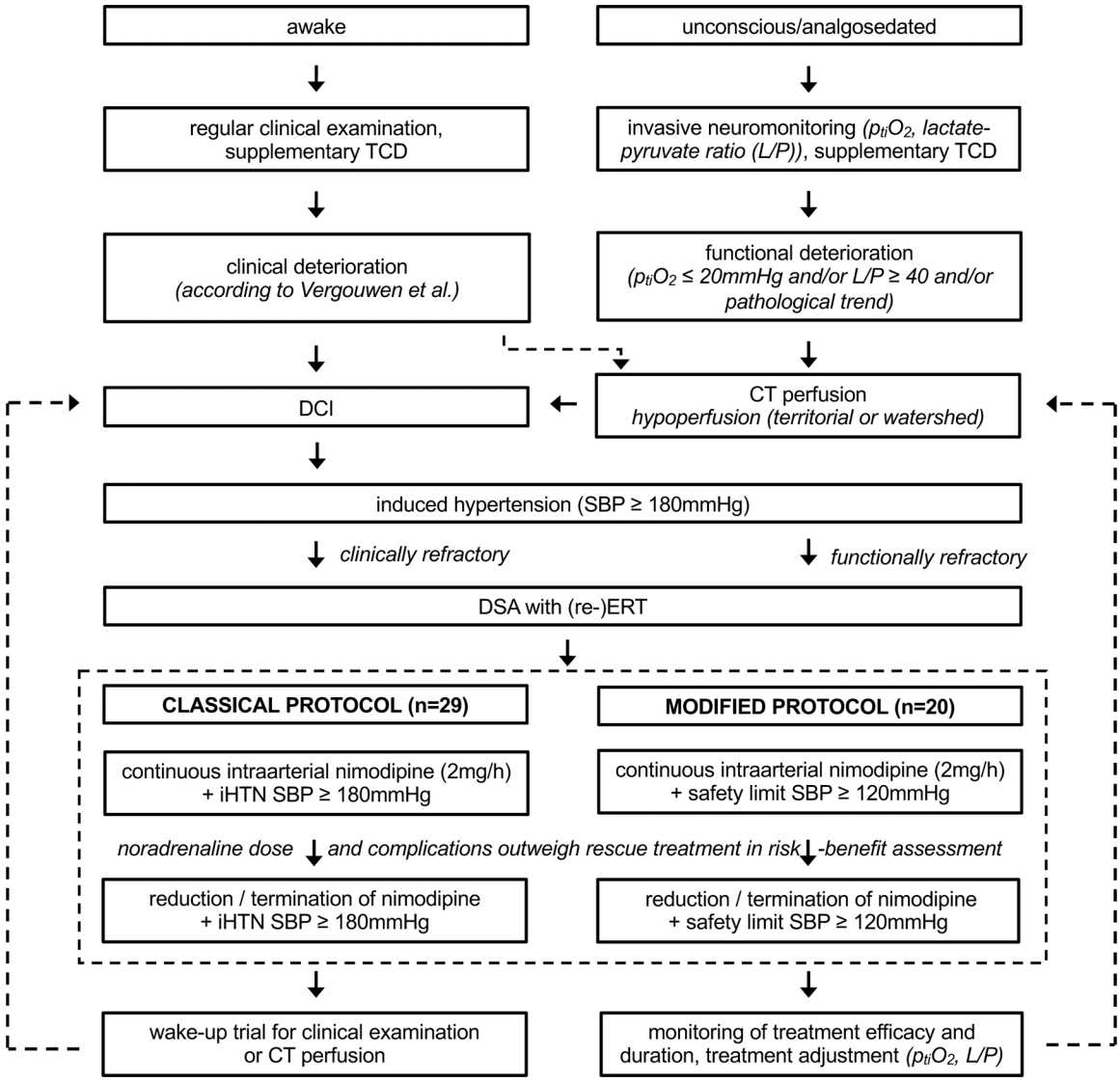

Figure 1.

Classical (iHTN+IAN) and modified (IAN_{only}) treatment protocols.

DCI: delayed cerebral ischemia; ERT: endovascular rescue treatment; iHTN+IAN: patients treated according to the classical protocol; IAN_{only}: patients treated according to the modified protocol; TCD: transcranial doppler ultrasonography; SBP: systolic blood pressure.

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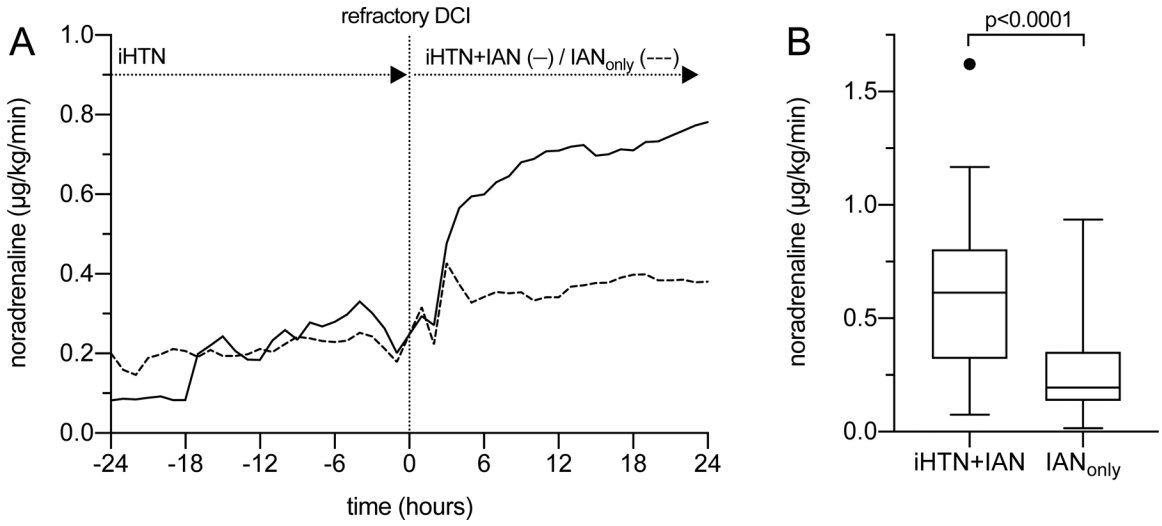

Figure 2.

Primary outcome (noradrenaline demand).

(A) Noradrenaline requirements were strongly increased 24 hours after initiation of IAN in patients treated with iHTN+IAN (0.23±0.32 to 0.67±0.56µg/kg/min, Wilcoxon rank sum test, $p<0.0001$). With IAN_{only}, demand was still elevated after initiation of IAN (0.21±0.17 to 0.36±0.30µg/kg/min, $p<0.05$) but the increase was more moderate than with iHTN+IAN ($p<0.05$). **(B)** Mean noradrenaline demand displayed as Tukey boxplot. The line in the middle of the box represents the median value, the box edges represent 25^{th} and 75^{th} percentiles, the whiskers represent all other values up to 1.5 times the interquartile range, outliers are shown as dots. Noradrenaline demand of the total treatment duration was significantly reduced with IAN_{only} (iHTN+IAN 0.70±0.54µg/kg/min, IAN_{only} 0.26±0.20µg/kg/min, $p<0.0001$).

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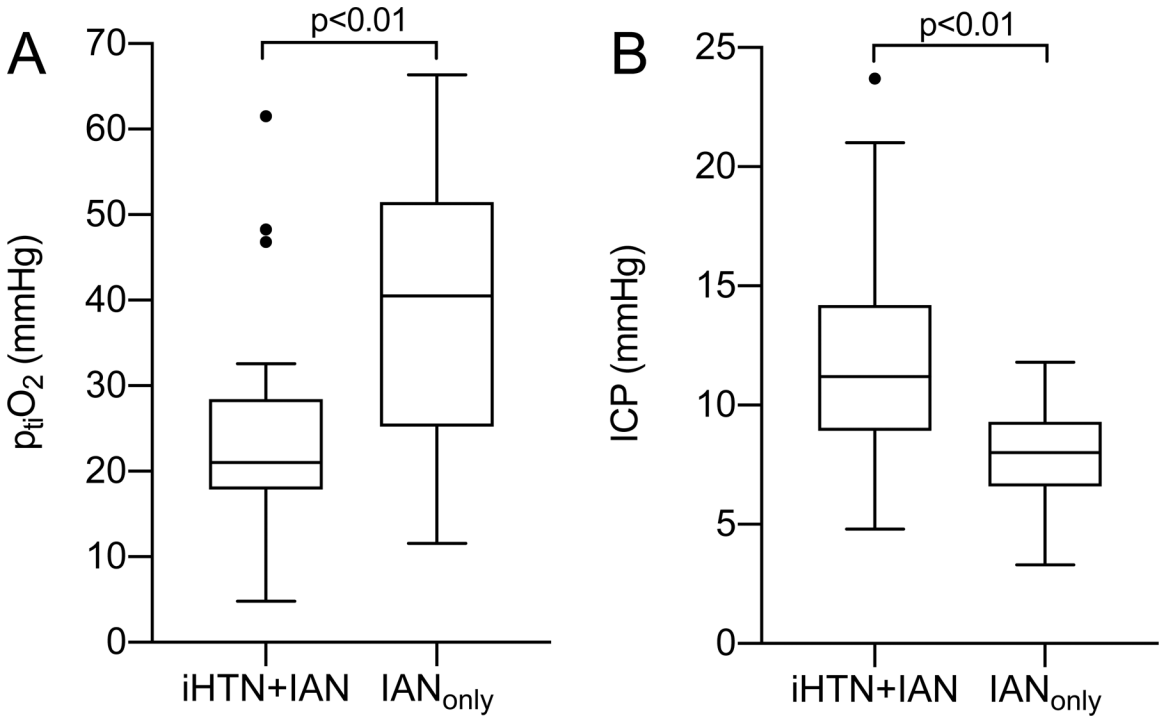

Figure 3.

Brain tissue oxygenation and intracranial pressure.

(A) Brain tissue oxygenation ($p_{ti}O_2$) and **(B)** intracranial pressure (ICP) calculated as means over the total treatment duration (neuromonitoring iHTN+IAN n=21 (72.4%), IAN_{only} n=11 (55.0%)) with significantly higher $p_{ti}O_2$ and lower ICP with IAN_{only}.

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Table 1.

Demography and bleeding characteristics.

	iHTN+IAN	IAN_{only}	p-value
n	29	20	
age, years	53.3±7.7	53.2±10.4	0.99
female sex, n (%)	20 (69.0%)	17 (85.0%)	0.31
body mass index	26.3±5.2	25.8±4.8	0.96
arterial hypertension, n (%)	12 (41.4%)	8 (40.0%)	1.00
smoking, n (%)	10 (34.5%)	9 (45.0%)	0.56
Hunt & Hess grade 4–5, n (%)	5 (17.2%)	6 (30.0%)	0.32
modified Fisher grade 3–4, n (%)	17 (58.6%)	15 (75.0%)	0.36
aneurysm in the anterior circulation, n (%)	24 (82.8%)	20 (100%)	0.07
modality of aneurysm occlusion			
clipping, n (%)	13 (44.8%)	9 (45.0%)	1.00
endovascular, n (%)	16 (55.2%)	11 (55.0%)	

Unpaired t-test or Mann-Whitney U test assessed differences between groups, as appropriate. Fisher's exact test was used for comparisons of discrete variables. iHTN+IAN: patients treated according to the classical protocol; IAN_{only}: patients treated according to the modified protocol.

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Table 2.

Secondary outcome parameters.

	iHTN+IAN	IAN_{only}	p-value	OR (95% CI)
safety (noradrenaline)				
coerced treatment de-escalations				
n (%) patients with ≥1 de-escalation	15 (51.7%)	7 (35.0%)	0.25	0.50 (0.16–1.62)
reduction (IAN or iHTN), n	34	11		
termination (IAN or iHTN), n	4	1		
noradrenaline dose triggering de-escalation, µg/kg/min	1.31±0.63	0.73±0.24	<0.01 *	
minor complications				
n (%) patients with ≥1 minor	14 (48.3%)	3 (15.0%)	<0.05 *	0.19 (0.05–0.79)
complication	13	3		
peripheral hypoperfusion, n	3	1		
cardiac arrhythmia, n				
major complications				
n (%) patients with ≥1 major complication	6 (20.7%)	4 (20.0%)	0.95	0.96 (0.23–3.95)
cardiac insufficiency, n	1	0		
myocardial infarction, n	0	0		
paralytic ileus or gut ischemia, n	2	3		
acute kidney failure, n	3	0		
SSC-CIP, n	0	1		
CT perfusion images during IAN, n	4.7±2.5	6.1±3.3	0.12	
efficacy (rescue treatment)				
mean $p_{ti}O_2$, mmHg	26.6±15.3	39.6±15.4	<0.01 *	
mean ICP, mmHg	12.0±5.0	8.1±2.3	<0.01 *	
≥1 treatment re-escalation, n (%)	17 (58.6%)	13 (65.0%)	0.65	1.31 (0.40–4.26)
duration of IAN, days	7.6±4.7	11.5±6.2	<0.05 *	
duration of iHTN, days	17.7±7.2	11.6±8.9	<0.01 *	
hospitalization, days	38.8±17.5	42.7±10.0	0.38	
DCI related infarction				
n (%) patients with ≥1 infarction	12 (41.1%)	9 (45.0%)	0.80	1.16 (0.37–3.66)
infarctions before iHTN, n	0	3		
infarctions during iHTN, before IAN, n	7	5		
infarctions during IAN, n	5	1		
infarctions after IAN, n	2	3		
Glasgow Outcome Scale 4–5 after 6 months, n (%)	10 (40.0%)	10 (55.6%)	0.32	1.88 (0.55–6.39)

Unpaired t-test or Mann-Whitney U test assessed differences between groups, as appropriate. Binary logistic regression analysis was used for comparisons of discrete variables.

*: significant p-value; DCI: delayed cerebral ischemia; ICP: intracranial pressure; iHTN+IAN: patients treated according to the classical protocol; IAN_{only}: patients treated according to the modified protocol; SSC-CIP: secondary sclerosing cholangitis in critically ill patients.