

Neuroprotective Treatment Strategies for Delayed Cerebral Ischemia after Subarachnoid Hemorrhage – Review of Literature and Future Prospects

Thomas Westermaier*

Department of Neurosurgery, University Hospital Wuerzburg, Josef-Schneider-Str. 11, 97080 Wuerzburg, Germany

Abstract

This article reviews experimental and clinical data on the use of various neuroprotective agents and therapeutic measures after aneurysmal subarachnoid hemorrhage (SAH). While calcium antagonists have been used in the past and are still part of the standard treatment regimen in most departments involved in the treatment of SAH, other classes of drugs and various other methods have been tested for their potential to inhibit delayed ischemia after SAH. This article reviews the literature about clinical studies about the efficacy of various neuroprotective agents and methods including statins, steroids and Endothelin-antagonists and other - alternative - methods like cisternal lavage, intrathecal drug delivery and hypercapnia, offering future perspectives for the treatment of this hazardous disease.

Keywords: Subarachnoid hemorrhage; Neuroprotection; Delayed cerebral infarction; Delayed ischemic neurological deficit

Introduction

Delayed ischemic neurological deficit (DIND) and delayed cerebral infarction (DCI) are the most important postoperative risk factors for poor outcome after aneurysmal subarachnoid hemorrhage (SAH) [1]. Aneurysmal SAH is associated with a total mortality of estimatedly 50% including patients who die before admission to a hospital. In spite of new diagnostic tools, modern intensive care therapy and early aneurysm occlusion, the in-hospital mortality has remained at 25% [2]. A large part of the surviving patients does not recover their pre-hemorrhage state [3]. Thus, SAH causes great personal harm and a great economical burden to health systems.

Early brain damage in the first minutes after rupture of an aneurysm cannot be treated or reversed, as it usually occurs outside hospital walls. Treatment can begin when emergency physicians or paramedics have the first contact with the patient. At first, only general measures of treatment can be undertaken like analgesic therapy, application of oxygen or sometimes intubation and mechanical ventilation. Targeted therapy can be initiated not before the diagnosis of SAH has been established by a CT-scan. Later in the course of the disease, the patients are threatened by delayed ischemic events which arise several days after aneurysm rupture. Concerning these delayed perfusion deficits; however, there is the unique opportunity to start therapeutic measures in advance, before cerebral blood flow (CBF) declines below ischemic thresholds [4]. Various forms of treatment have been tested and used to enhance CBF and protect the brain from ischemic deficits. Among these, different calcium antagonists are the most prominent substances. Following the growing knowledge about pathophysiological mechanisms, a variety of further agents have been tested for their therapeutic efficacy.

Pathophysiology

Aneurysmal SAH is characterized by 3 different forms of cerebral ischemia. First, global ischemia develops immediately after aneurysm rupture. The extravasation of blood into the subarachnoid space causes an increase of intracranial pressure (ICP) and subsequently a decrease of cerebral perfusion pressure (CPP). This stage of the disease cannot be therapeutically influenced because it occurs outside hospitals and before the diagnosis of SAH is established. An acute global vascular reaction also arises in the first seconds or minutes after aneurysm

rupture, affects the entire cerebral vasculature at least for several hours even when CPP has recovered to normal [5].

In the following days, a variety of local factors lead to endothelial dysfunction and changes in the contraction state of the vessels. They finally lead to structural changes of the vessel wall with intimal thickening and media proliferation [6]. Several days after SAH, delayed vasospasm develops in up to 70% of all patients who suffered from SAH. Until now, the exact pathogenesis is not clarified. Inflammatory processes are involved in this phenomenon and contribute to arterial narrowing [7]. The amount of subarachnoid blood is a good prognostic factor for the development of cerebral vasospasm and DIND indicating that hemoglobin in the subarachnoid space is the antigen that causes inflammatory reactions [8,9].

Nitric oxide (NO) induces the generation of cyclic guanosyl monophosphate (cGMP) which results in vasodilatation by several mechanisms [10,11]. Due to its high affinity, NO binds to hemoglobin, resulting in an NO-depletion. The number of perivascular neurons which carry relatively high amounts of NO and supply the large intracranial vessels, is decreased after SAH causing a further decrease of NO [12,13].

Free radicals are produced after SAH by a decay of leukocytes and by autooxidation of hemoglobin [7,14]. The degradation of membrane proteins and lipids are the consequence of the free radical activity resulting in a damage of endothelial cells, smooth muscle cells and perivascular neurons. Vasoactive substances are liberated, especially arachidonic acid metabolites. A direct inflow of calcium into vascular smooth muscle cells may be caused by a damage of the membrane integrity.

Hemoglobin induces a radical-mediated damage of the cell

***Corresponding author:** Thomas Westermaier, University Hospital Wuerzburg, Department of Neurosurgery, Josef-Schneider-Str. 1197080 Wuerzburg, Germany, Tel: +49-931-24527; Fax: +49-931-24551; E-mail: westermaier.t@nch.uni-wuerzburg.de

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membrane and an activation of Phospholipase A₂. Finally, a shift towards constrictive arachidonic acid metabolites occurs. The level of prostacyclin is reduced in the cerebral spinal fluid (CSF) of SAH-patients who develop delayed vasospasm [15].

Endothelin-1 is the most powerful vasoconstrictive factor known to date. It has been found to be elevated in blood and CSF of patients who develop vasospasm after SAH. The elevation of Endothelin-1 levels correlate with the severity of vasospasm [16].

The extravasation of hemoglobin into the subarachnoid space is a toxic stimulus. The immune system reacts with a specific answer. Several hours after SAH, cellular adhesion molecules are found on the luminal surface of endothelial cells [17]. An inflammatory cascade develops, including the adhesion and extravasation of leukocytes. Different from other types of tissue, there is no clearance of the subarachnoid space by the lymphatic system. Therefore, leukocytes decay and vasoactive substances like Endothelin-1 and free radicals are set free. Cerebral vasospasm is likely not to be monofactorial.

Today all these processes are thought to be factors of the development of arterial narrowing which is probably the basis of secondary ischemia evolving several days after aneurysmal SAH. However, arterial vasospasm seems not to be the only factor for the development of DCI after SAH. It has been shown that - although less frequently - DCI after SAH can occur without significant cerebral vasospasm [18]. On the other hand, the number of patients suffering from arterial vasospasm is much higher than the number of patient's developing DCI [19]. Additional pathophysiological mechanisms have been proposed to induce secondary ischemia after SAH. Dreier et al. [20] and Pluta et al. [21] suggested a double-hit model of secondary ischemia in which mechanisms causing ion disturbances and hypermetabolism are superimposed on arterial narrowing and, in combination, cause DCI. Although the aetiology of DCI is not exactly known, all pathophysiological factors are likely to finally turn into a discrepancy between the supply and demand of oxygen in the brain. Following the growing knowledge about pathophysiological mechanisms, several attempts have been conducted to treat or prevent secondary ischemia after SAH and improve the outcome of SAH-patients.

Evidence for Drug Effectiveness in Clinical Trials

There is, at present, no specific agent or method that has proven clear efficacy for the treatment of early ischemia after SAH. The early management of SAH-patients includes intubation and mechanical ventilation if normal ventilation and oxygenation are at risk, ventriculostomy in case of occlusive hydrocephalus, medical treatment of elevated intracranial pressure (ICP), and early treatment of the aneurysm by surgical clipping or endovascular coiling, moderate hyperdynamic therapy to secure cerebral perfusion and the avoidance of medical complications. As secondary ischemic events after SAH occur with a delay of several days, there is the chance to start a specific neuroprotective treatment prior to ischemia. This is decisively different to embolic stroke which hits the patient at home or "in the field", in most cases without prior warning signals [22]. A variety of substances have been tested in clinical trials.

Corticosteroids

Inflammatory reactions are believed to be a decisive factor for the development of arterial narrowing after SAH [7,17]. Corticosteroids have an antiinflammatory effect, stabilize cell membranes and address the radical-induced cell damage and the effect of the calcium-influx into

endothelial cells, smooth muscle cells, neurons and glial cells mediated by Phospholipase A₂. The effectiveness of a high-dose therapy with corticosteroids after aneurysmal SAH, however, is not clarified to date. The mineralocorticoid fludrocortisone [23,24] and the glucocorticoid hydrocortisone [25] have been tested in clinical studies. In a meta-analysis, the therapy with corticosteroids did not show a distinct benefit for the patients [26]. Separately analyzed, the treatment with mineralocorticoids resulted in less ischemic complications. Serious side effects like gastrointestinal bleedings and electrolyte imbalance prevented a beneficial effect on outcome parameters in the treatment with hydrocortisone. In summary, the number of patients included in these three clinical trials is too small (256 patients) and the studies too inhomogenous to indicate a clear benefit of a corticosteroid treatment. Recently, a randomized, placebo-controlled clinical trial was published in which 95 patients with aneurysmal SAH received methylprednisolone in a daily dose of 16 mg/kg body weight for 3 days. The treatment resulted in an improvement of clinical outcome which nearly reached the level of significance [27].

Tirilazad

Tirilazad mesylate is a 21-aminostroid with only very little mineralo- and glucocorticoid activity. It acts as a radical scavenger and membrane protector [28]. The substance inhibits the free radical-mediated damage of endothelial membranes and neurons. After promising results in experimental studies several clinical trials were conducted. In all of these studies, patients were co-treated with the calcium antagonist nimodipine. A meta-analysis showed that the delayed arterial narrowing was reduced by treatment with tirilazad. However, this effect was not accompanied by a significant reduction of DCI and improvement of neurological outcome [29].

Statins

Hydroxymethylglutaryl coenzyme A reductase inhibitors, so-called "statins", have a variety of properties which may potentially inhibit cerebral vasospasm. Among those are antiinflammatory activity and endothelial cell protection. Several clinical trials have been conducted. Early clinical studies revealed a lower incidence of cerebral vasospasm, vasospasm-related neurological deficits and mortality [30,31]. However, these trials were small and the end points varied strongly. More recent trials reported less promising results as they could not clearly reproduce the positive effects on vessel narrowing, DCI and neurological outcome [32,33]. The attempt to generate a Cochrane Review failed due to the poor quality of some trials and the inhomogeneity of the available trials [34]. A closing statement about the usefulness of a statin treatment after SAH cannot be drawn. Further trials are on the way [35,36].

Endothelin-receptor antagonists

Three randomized clinical studies have been published in literature. One trial investigated a non-selective (ET_A/ET_B) Endothelin-receptor antagonist (TAK-044), two investigated the selective ET_A-receptor antagonist Clazosentan [37-39]. The objective was to antagonize the strong vasoconstrictive activity exerted by ET_A-receptors as Endothelin-1 concentrations are elevated in both blood and CSF of SAH-patients who develop delayed cerebral vasospasm.

A total of 867 patients was included in these trials. The treatment resulted in a distinct reduction of arterial narrowing (Odds Ratio (OR) 0.31). The incidence of DCI was less pronounced (OR 0.68) and there was only a marginal improvement of neurological outcome, determined as good (Glasgow outcome scale (GOS) 4 and 5) versus bad (GOS 1-3) outcome (OR 0.87). Mortality was even increased (OR 1.09)

[40]. The discrepancy between delayed cerebral vasospasm and DCI may be explainable by a hypotensive effect of ET_A -receptor antagonists, which may prevent an improvement of cerebral perfusion in spite of attenuated arterial narrowing. The discrepancy between the reduced incidence of DCI and the failure to improve clinical outcome and even increased mortality may be explained by serious systemic side effects like pneumonia and pulmonary edema [40].

Calcium antagonists

In the 1980s and 1990s, a series of clinical trials was conducted to test the efficacy of pyrrolopyrimidine-type calcium antagonists. These substances were applied to inhibit cellular calcium influx in cerebrovascular smooth muscle cells via voltage-dependent L-type calcium channels which were suspected to be responsible for the occurrence of delayed cerebral vasospasm after SAH. It was registered rather quickly, that this kind of treatment did not prevent or dissolve arterial vasospasm. In a British clinical multicenter trial, however, a reduced incidence of DCI and improvement of clinical outcome by the oral treatment with nimodipine was observed [41]. Although this was the largest clinical trial, it was the only one that observed a significant benefit. A series of other trials with nimodipine and other calcium antagonists failed to reduce the incidence of DCI and improve outcome after SAH. A Cochrane Review edited in 2007 analyzed 7 prospective, randomized, placebo-controlled clinical trials with nimodipine and recommended its prophylactic administration in SAH-patients. However, the authors concluded that this recommendation was not “beyond any doubt”. If the above mentioned British multicenter trial was taken out of the statistical analysis, no more benefit over a placebo-treatment could be calculated [42].

The prophylactic treatment with nimodipine has become a standard therapy in many centers. However, its standard use must be critically reviewed as there is a variety of conflicting issues regarding nimodipine. There is no evidence for the intravenous use, which was initially promoted by the manufacturer. The information about the oral uptake of the agent is scarce. In patients who are mechanically ventilated, oral nimodipine has to be administered via a stomach tube. Especially in the weaning phase after several days of mechanical ventilation, which parallels in many cases the period of maximum vasospasm, gastral reflux makes the uptake of orally administered substances incalculable. Nimodipine can cause hypotension and can open pulmonary arteriovenous shunts resulting in oxygenation problems. Finally, the meta-analyses about the use of calcium antagonists that are available today, refer to clinical trials that were conducted more than 25 years ago. The objective for a treatment with nimodipine and other calcium antagonists was the avoidance of delayed cerebral perfusion deficits. In the past 25 years, however, intensive care therapy has improved, many aneurysms are treated by endovascular coiling, and endovascular balloon dilatation and pharmacological vasospasmolysis are used to treat critical arterial narrowing of cerebral vessels and improve CBF [43]. The prerequisites have changed and it is doubtful whether a prophylactic oral treatment with nimodipine would still exert a beneficial effect under modern treatment standards [44].

Magnesium sulfate

Magnesium has been called “nature’s physiologic calcium blocker” as it is a physiological mineral and interferes with calcium in a variety of ways [45]. The bivalent magnesium cation can compete with calcium ions for receptor binding or passage through ion channels. It dilates blood vessels by competitive inhibition of voltage-dependent calcium channels in vascular smooth muscle cells [46], improves rheological

functions by inhibition of platelet aggregation [47,48], and increases the deformability of red blood cells [49]. Under experimental conditions, it prevents cellular calcium influx and excitatory amino acid release in neurons by blockade of N-type and L-type calcium channels [50], prevents cellular calcium entry through NMDA-receptor channels [51], reduces calcium-induced mitochondrial dysfunction [52] and preserves cellular energy metabolism [53]. By these mechanisms, magnesium may inhibit or delay ischemic cell death during and after cerebral ischemic events.

Low blood pressure is a risk factor for aggravation of ischemic damage in states of cerebral ischemia reducing collateral flow in the ischemic penumbra. Therefore, magnesium doses must be kept low enough to ensure stable blood pressure if it is administered for the purpose of neuroprotection. In an experimental study of temporary middle cerebral artery occlusion (MCAO) in rats, serum concentrations of 2.0-2.5 mmol/l showed the highest neuroprotective effect [54]. In higher doses, the cardiodepressive effect seems to limit the extent of neuroprotection.

The potential role for a treatment with magnesium was supported by the observation that hypomagnesemia is frequently found in SAH patients and correlates with the amount of blood in the subarachnoid space and with the patient’s neurological condition at the time of hospital admission. Hypomagnesemia arising during the course of treatment, in turn, correlates with the appearance of secondary neurological deficits and ischemic infarctions [55]. A series of clinical trials has been launched to assess the ability to reduce secondary neurological deficits after SAH. Several small observational studies and placebo-controlled studies using different doses of intravenous magnesium sulfate produced promising results [56-61]. In a randomized, placebo-controlled multicenter study conducted by van den Bergh et al., patients received a daily dose of 64 mmol $MgSO_4$ for 14 days. The results were promising. Magnesium treatment reduced the risk of DCI by 34% and the risk for poor outcome by 23%. Including 283 patients, however, the study was still underpowered [62]. In a south-east Asian/Australian trial, 327 patients were randomized to receive placebo or a daily dose of 80 mmol/l $MgSO_4$. The authors reported no significant benefit of magnesium-treatment regarding DCI and neurological outcome after 6 months [63]. The largest clinical trial has been conducted by Mees et al. In this multicenter trial, 1,204 patients with aneurysmal SAH were enrolled and randomized to receive 64 mmol $MgSO_4$ per day or placebo. The administration of $MgSO_4$ did not improve clinical outcome at an end point 3 months after SAH [64].

These results also require a critical analysis. Except for a very small early clinical trial conducted by Luo et al. [56], who compared magnesium treatment to a true placebo group, all patients enrolled in these trials were co-treated with nimodipine. The authors of the latter studies conclude that intravenous magnesium fails to improve neurological outcome and mortality in spite of decreasing the incidence of DCI [65]. Among the trials, magnesium doses varied significantly. However, it is noticeable that all studies that found no benefit of magnesium-treatment used nimodipine as a “standard-treatment” which was administered to both the treatment-group and the “control-group”. Schmid-Elsaesser et al. compared treatment with magnesium to treatment with nimodipine. Patients of the magnesium-group did not receive nimodipine. The authors did not register a significant difference between the two treatments arms [66]. In our own study, magnesium-therapy was compared to a true placebo-group and resulted in a significant improvement of DCI and arterial spasm. Nimodipine was given to neither of both groups [67]. The combined administration

of magnesium and nimodipine is a combination therapy with two calcium antagonists. Therefore, it is not surprising that this treatment does not result in an additional effect as it is commonly known that the effect of a combination therapy is not necessarily the sum of its single components, in particular if both drugs have - in part or in total - the same mechanisms of action. The doses and co-medications vary too much to finally judge at this point whether magnesium may be an effective drug after aneurysmal SAH.

In summary, the pharmacological attempts that have been conducted in the past were disappointing. The number of high-quality studies testing the efficacy of corticosteroids and statins is too small to supply evidence for their use in SAH-patients [25,34], radical scavengers and Endothelin-receptor antagonists have shown a positive effect regarding the treatment of delayed cerebral vasospasm but resulted in no improvement of DCI and neurological outcome [29,30]. Nimodipine has become a standard treatment on many centers although its use is not “beyond any doubt” as a Cochrane Review has stated [42]. Furthermore, the data on which the evidence for nimodipine-treatment bases, is more than 25 years old. In the meantime, treatment of aneurysms and vasospasm has been improved and a re-evaluation of nimodipine under new treatment standards must be called for [44]. Magnesium is cheap and safe to handle. However, recent trials have not found a significant protective effect if administered in addition to nimodipine [63,64]. If given without co-treatment with other calcium antagonists, it has shown a protective effect and might still be a promising substance in SAH-patients [66,67]. Due to these disappointing results, alternative methods may be interesting for the treatment of secondary ischemia after aneurysmal SAH.

Alternative Treatment Strategies and Future Prospects

Various attempts other than the systemic - oral or intravenous - administration of drugs have been conducted in order to treat delayed cerebral vasospasm and DCI. Some of these may have a high potential to become important forms of treatment.

Subarachnoid washout

Subarachnoid blood or - more precisely - hemoglobin is the antigen that induces inflammatory reactions which ultimately lead to changes in the vessel walls and arterial narrowing [7]. The amount of subarachnoid blood determines the extent of delayed cerebral vasospasm [8]. In

animal studies, the injection of blood into the subarachnoid space reproducibly leads to cerebral vasospasm with a delay of several days [68]. The removal of the subarachnoid blood clot may prevent or alleviate cerebral vasospasm if it is performed early enough [69,70]. In the practical setting, however, a complete or near-complete removal of the subarachnoid blood clot during aneurysm surgery seems too dangerous and is not reasonable. Several studies have been conducted to dissolve the blood clot by fibrinolytic agents. First clinical experience was gathered in the 1980s. Tsementzis et al. reported that this method is safe in SAH-patients [71]. In a small number of patients, Hamada et al. administered urokinase via an intrathecal catheter and found a complete removal of the subarachnoid blood clot as visible in CT-scans within 24 hours. None of these patients developed DCI [72]. Yamamoto et al. administered tissue plasminogen activator (tPA) continuously or intermittently via a cisternal catheter which was positioned during surgical clipping of the aneurysm and compared two treatment-groups (continuous or intermittent administration) to a control group. The authors found no relevant risks of intrathecal fibrinolytic therapy, a reduction of ischemic events and an improvement of neurological outcome in the treatment-groups favoring the intermittent administration [73]. The patient collectives were too small to draw firm conclusions. However, the absence of side effects and the positive results with regard to secondary ischemic events make intrathecal fibrinolytic therapy a promising treatment.

Continuous head motion and rotational therapy for subarachnoid lavage

The objective of this manipulation is to accelerate the washout of blood by a continuous motion of the head. This form of treatment was first described by Suzuki et al. in 1990 and later picked up by Kawamoto et al. [74,75]. Kawamoto et al. reported about a marked reduction of delayed vasospasm, DIND and DCI and an improvement of neurological outcome by continuous head motion combined with cisternal irrigation. Eicker et al. combined continuous low-frequency head motion with fibrinolytic therapy in 40 patients and reported a significant decrease of DCI [76].

Intrathecal delivery of vasodilators

To date, the intrathecal administration of vasodilators, calcium antagonists (Table 1) and sodium nitroprussid (SNP) (Table 2) has been performed in particular cases with cerebral vasospasm which is

Author	Agent and application	Patient collective	Results	Methodical side effects	Pharmacological side effects	Remark
Shibuya et al., 1994 [84]	Nicardipine via cisternal catheter (3 x 2 mg daily from day 10-17)	Patients with high risk of vasospasm (Fisher grade 3) (50 treatment, 91 control)	50% reduction of DIND, reduction of angiographic vasospasm	2 Meningitis	Headache	Not randomized
Suzuki et al., 2001 [85]	Nicardipine via cisternal catheter (2 x 4 mg from day 3-14)	177 consecutive SAH patients	Low rate of angiographic vasospasm and DIND	6% meningitis	None	No controlled study
Fujiwara et al., 2001 [86]	Nicardipin via cisternal catheter (continuous administration of 8 mg daily for 14 days)	5 patients with high risk of vasospasm	No angiographic vasospasm, reversible DIND in 1 patient	1 meningitis	None	No controlled study
Etisham et al., 2008 [87]	Nicardipin via EVD (2 x 4 mg daily over several days)	6 patients with vasospasm	Marked reduction of flow velocity in TCD after nicardipine administration in 5 patients	None	None	No controlled study
Goodson et al., 2008 [88]	Nicardipin via EVD (2 x 4 mg daily over 5-17 days)	8 patients with refractory vasospasm	Good outcome in 7 patients, death in 1 patients	None	headache in 1 patient	No controlled study
Hänggi et al., 2008 [89]	Nimodipine (0.4 mg bolus via EVD followed by continuous infusion of 0.4 mg/h via lumbar drainage)	8 patients with refractory vasospasm	Immediated improvement in 3 patients, improved perfusion (Perfusion-CT) in 70%. Improved angiographic vasospasm in 7 patients.	1 meningitis	None	No controlled study

Table 1: Clinical studies on the treatment of cerebral vasospasm with calcium antagonists via cisternal or ventricular catheters (DIND=delayed ischemic neurological deficit, TCD=transcranial Doppler sonography).

Author	Agent and application	Patient collective	Results	Methodical side effects	Pharmacological side effects	Remark
Thomas et al., 1999 [90]	SNP via EVD or cisternal catheter Group 1: 7-88 mg SNP until improvement of spasm or occurrence of side effect Group 2: 4-8 mg SNP every 6 hours for 5-17 days	Group 1: 15 patients with refractory vasospasm Group 2: 10 patients prophylactically (Fisher grade 3, Hunt/Hess grade 3-5)	Group 1: improvement of angiographic vasospasm in 8 patients Group 2: no signs of vasospasm	None	Group 1: hypotension in 3 cases, nausea in 2 cases Group 2: None	No controlled study, not randomised
Thomas et al., 2002 [91]	SNP+Thiosulfat via EVD (4 mg/ml und 10 mg/ml) "acute protocol": 10 ml in 10 single doses every 5 minutes "prophylactic protocol": 2 ml over 60 minutes for 11-14 days	"acute protocol": 10 patients with DIND or elevated flow velocities in TCD "prophylactic protocol": 6 patients	Improvement of DIND and flow velocities in TCD in 9/10 cases	None	None	No controlled study
Raabe et al., 2002 [92]	SNP via EVD or cisternal catheter single bolus 10-40 mg (11 patients) continuous infusion 2-8 mg for 7-14 days	13 patients with refractory vasospasm	Tissue oxygenation improved in 6 patients with vasospasm	None	Hypotension in 5 cases, nausea in 3 cases, cardiac arrhythmias in 1 case	No controlled study, not randomized
Pathak et al., 2003 [93]	SNP "high-dose" (5 mg every 4-12 hours via EVD) SNP "low-dose" (4 mg every 6 hours via cisternal catheter)	"high-dose": 5 patients with DIND "low-dose": 3 patients with SAH Fisher grade 3	reduction of flow velocity in TCD No spasm in 2, moderate spasm in 1 prophylactically treated patients	None	Distinct hypotension after administration of SNP	Not randomised
Kumar et al., 2003 [94]	SNP via EVD Repeated administration of 4 mg bolus	10 patients with SAH	improvement or complete recovery of vasospasm in all patients	None	Nausea in higher doses, hypotension in 2 cases	No controlled study, not randomized

Table 2: Clinical trials assessing the effects of intrathecal administration of sodium nitroprussid in patients with refractory vasospasm and patients with high risk to develop vasospasm and DCI (SNP=sodium nitroprussid, EVD=external ventricular catheter, TCD=transcranial Doppler sonography).

Author	Agent and Application	Patient Collective	Results	Methodical Side Effects	Pharmacological Side Effects	Remark
Dalbasti et al., 2001 [95]	Papaverin pellets intraoperative positioning of pellets	117 patients with high risk of vasospasm (73 treatment, 44 control)	marked reduction of vasospasm, significant improvement of outcome	None	None	No randomisation
Kasuya et al., 2005 [96]	Nicardipin pellets, intraoperative positioning of pellets	125 patients with high risk of vasospasm (97 treatment, 28 control)	mignificant reduction of DIND	None	None	No randomisation
Krischek et al., 2007 [97]	Nicardipine pellets intraoperative positioning of pellets	100 patients with high risk of vasospasm (Fisher grade 2 und 3)	7 patients with DIND, 5 patients with DCI. No spasms in vicinity to pellets	None	None	No randomisation
Barth et al., 2007 [98]	Nicardipine pellets, intraoperative positioning of pellets	32 patients (16 treatment, 16 control)	reduction of angiographic vasospasm and DIND, improvement of neurological outcome	None	None	Randomized study

Table 3: Clinical studies assessing the efficacy of intraoperatively positioned drug-releasing "pellets" containing vasodilating agents (DIND=delayed ischemic neurological deficit).

refractory to medical and endovascular treatment or prophylactically in patients who were considered to have a particularly high risk to develop delayed cerebral vasospasm and DIND. Apart from this, nicardipine, a calcium antagonist was prophylactically attached to cerebral vessels during surgical clipping of aneurysms in the shape of "pellets" which dissolve slowly and continuously release the agent (Table 3). The results were reproducibly positive as intrathecal therapy tended to prevent vasospasm and even reverse vasospasm which was refractory to medical treatment. However, there is no randomized, placebo-controlled trial which supplies good evidence for intrathecal treatment.

Again, magnesium may be a promising substance for intrathecal administration. It is a physiological component of CSF and a moderate increase of its CSF concentration is unlikely to produce serious side effects. Furthermore, the CSF concentration can easily be followed by laboratory analyses. However, experimental studies suggest that CSF concentrations of 2-4 mmol/l are necessary to dilate spastic vessels [77,78]. These concentrations cannot be produced by an intravenous administration of magnesium sulfate since the systemic side effects

could be hazardous. Mori et al administered magnesium sulfate via a cisternal catheter in patients with cerebral vasospasm refractory to other forms of therapy and found a reduction of the extent of arterial narrowing [79], measured by transcranial Doppler sonography.

Carbon dioxide

Cerebral autoregulation upon changes of arterial blood pressure is deranged after aneurysmal SAH. The cerebrovascular reactivity on changes of arterial CO₂ concentrations, however, may be altered but is still preserved [80,81]. It is well known that hyperventilation enhances cerebral perfusion deficits after SAH and induces ischemia [82].

A series of studies has been published investigating the reactivity of CBF on changes of arterial CO₂ concentrations and their prognostic relevance for the development of DCI after SAH. Recently, Carrera et al. found that decreased cerebrovascular reactivity on changes of arterial CO₂ is associated with a higher risk to develop cerebral ischemia [83]. Until now, this basic physiological regulation mechanism has not been

used therapeutically, although hypercapnia by inhalation of CO₂ or by reduction of the respiratory volume in mechanically ventilated patients may rapidly cause an enhancement of CBF. There may be a therapeutic potential to treat patients in a state of critical brain perfusion. A clinical trial investigating this phenomenon is currently on the way (www.clinicaltrials.gov, ID: NCT01799525).

A variety of interesting clinical trials has investigated alternative methods to treat delayed cerebral vasospasm after aneurysmal SAH. The numbers are too small and the investigations not structured enough to implement them into standard therapy yet. However, there may be a high therapeutic potential in these methods and possibly their combinations to treat patients in this critical condition.

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