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Julian Feulner, Cornelia S. Weidinger, Arnd Dörfler, Torsten Birkholz, Michael Buchfelder, Björn Sommer

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Early Intravenous Magnesium Sulfate and Its Impact on Cerebral Vasospasm as well as Delayed Cerebral Ischemia in Aneurysmal Subarachnoid Hemorrhage: A Retrospective Matched Case-Control Analysis

Julian Feulner[1,4], Cornelia S. Weidinger[2], Arnd Dörfler[3], Torsten Birkholz[2], Michael Buchfelder[1], Björn Sommer[1,5]

■ BACKGROUND: **Magnesium sulfate ($MgSO_4$) is a potential neuroprotective agent for patients with aneurysmal subarachnoid hemorrhage (SAH). We analyzed the effect of early application of intraoperative intravenous $MgSO_4$ and compared cerebral vasospasm (CV), delayed cerebral ischemia (DCI), and neurological outcome in 2 patient cohorts.**

■ METHODS: **A retrospective matched-pair analysis from patients at a single center in Germany was performed without (group A) and with (group B) $MgSO_4$ application <24 hours after diagnosis. Pairs were matched according to the known risk factors for DCI and CV (age, Fisher grade, smoking, severity of SAH). Incidence of CV and DCI and neurological outcome using the modified Rankin Scale score 3 and 12 months after SAH were recorded.**

■ RESULTS: **The inclusion criteria were met by 196 patients. After risk stratification, 48 patients were included in the final analysis (age 54.2 ± 8.1 years; 30 women and 18 men) and were assigned to group A ($n = 24$) or group B ($n = 24$). CV occurred less frequently in group B (33%) than in group A (46%). Likewise, DCI was present in 13% in group B compared with 42% in group A. After 12 months, 22 patients in group B had a favorable functional outcome (modified Rankin Scale score 0–3) compared with 15 patients in group A.**

■ CONCLUSIONS: **In this study, the incidence of CV and DCI was lower in patients receiving intravenous $MgSO_4$ within 24 hours after aneurysmal SAH onset. Favorable functional outcome was more likely in the $MgSO_4$ group after 12 months of follow-up.**

INTRODUCTION

In a systematic review and meta-analysis, the crude worldwide incidence of aneurysmal subarachnoid hemorrhage (aSAH) declined from 10.2 per 100,000 person-years in 1980 to 6.1 per 100,000 person-years in 2010.[1] A life-threatening disease of the central nervous system, aSAH affects adults 40–60 years of age in approximately 60% of all subarachnoid hemorrhage (SAH) cases. Despite best medical care, the in-hospital mortality is reported as 18%–21% according to recent series.[2-4] Besides the severity of the hemorrhage itself, secondary complications such as cerebral vasospasm (CV) or delayed cerebral ischemia (DCI) may induce brain tissue damage leading to neurological deterioration in up to 30% of patients.[5,6] Since the discovery of the neuroprotective effect of magnesium sulfate ($MgSO_4$) in the 1980s,[7,8] it is known that hypomagnesemia can occur in up to 50% of patients with aSAH and increases the risk of CV and DCI.[9] Patients with hypomagnesemia had higher aneurysmal rupture rates, and in patients with SAH, more extensive intracerebral hemorrhage was

Key words
- Aneurysmal subarachnoid hemorrhage
- Cerebral vasospasm
- Delayed cerebral ischemia
- Functional outcome
- Magnesium sulfate

Abbreviations and Acronyms
aSAH: Aneurysmal subarachnoid hemorrhage
CSF: Cerebrospinal fluid
CT: Computed tomography
CV: Cerebral vasospasm
DCI: Delayed cerebral ischemia
DSA: Digital subtraction angiography
MgSO4: Magnesium sulfate
mRS: Modified Rankin Scale
RCT: Randomized controlled trial
SAH: Subarachnoid hemorrhage
WFNS: World Federation of Neurosurgical Societies

From the Departments of [1]Neurosurgery, [2]Anesthesiology, and [3]Neuroradiology, University Hospital Erlangen, Erlangen; [4]Department of Neurosurgery, Klinikum Fürth, Fürth; and [5]Department of Neurosurgery, University Hospital Augsburg, Augsburg, Germany

To whom correspondence should be addressed: Björn Sommer, M.D. [E-mail: bjoern.sommer@uk-augsburg.de]

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diagnosed.[10-12] Thus, prevention of hypomagnesemia is recommended in these patients.[13]

However, several randomized controlled trials (RCTs) have not verified the clinical benefit of $MgSO_4$ therapy regarding functional neurological outcome in patients with aSAH, although the rate of vasospasm was significantly reduced.[14] Recent studies indicate that the neuroprotective effect depends on the timing of application as well as $MgSO_4$ levels in blood serum and cerebrospinal fluid (CSF).[12,15-18] The aim of this study was to analyze if the incidence of CV and DCI in aSAH is decreased by early intravenous application of $MgSO_4$. We also investigated the impact of $MgSO_4$ on functional neurological status.

MATERIALS AND METHODS

We performed a monocentric retrospective matched case-control study of patients who underwent microsurgical or endovascular treatment of a ruptured cerebral aneurysm. At the Department of Neurosurgery, University Hospital Erlangen, Germany, 2 different time periods (2003–2005 and 2014–2016) were observed, and 840 patients were screened using digital patient charts (Figure 1). Eligibility criteria are shown in Figure 2. Matching criteria included the known risk factors that are associated with CV (smoking and arterial hypertension)[19] and with DCI (age, Fisher grade, and clinical condition at admission).[14,20]

This study was performed in accordance with the Ethics committee of the Friedrich-Alexander University Erlangen-Nuremberg and with the 1964 Helsinki declaration and its amendments. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement was used as a reporting guideline.[21] Patient consent was neither required nor sought as the treatment with $MgSO_4$ is a standard operating procedure of our department.

Up to January 2006, the only routinely used drug for CV prevention was intravenous nimodipine with a starting dose of 1 mg/hour to a maximum of 2 mg/hour, depending on the hypotensive reaction. Due to paradigm changes based on the available scientific data available at that time, early intravenous administration of $MgSO_4$ was routinely established over the years. The period 2014–2016 was chosen due to a change in the picture archiving and communication system and patient administration system of the Departments of Anesthesiology, Neuroradiology, and Neurosurgery. The amendments provided a complete availability of data, which was obligatory for the statistical analysis.

Medical Treatment

As a rule, $MgSO_4$ was given at the beginning of either microsurgical or endovascular treatment, which was within 24 hours after establishing a diagnosis in general. The protocol included $MgSO_4$ 10% application with a loading dose of 50 mg/kg body weight over 1 hour. The infusion rate (20–40 mmol) depended on blood

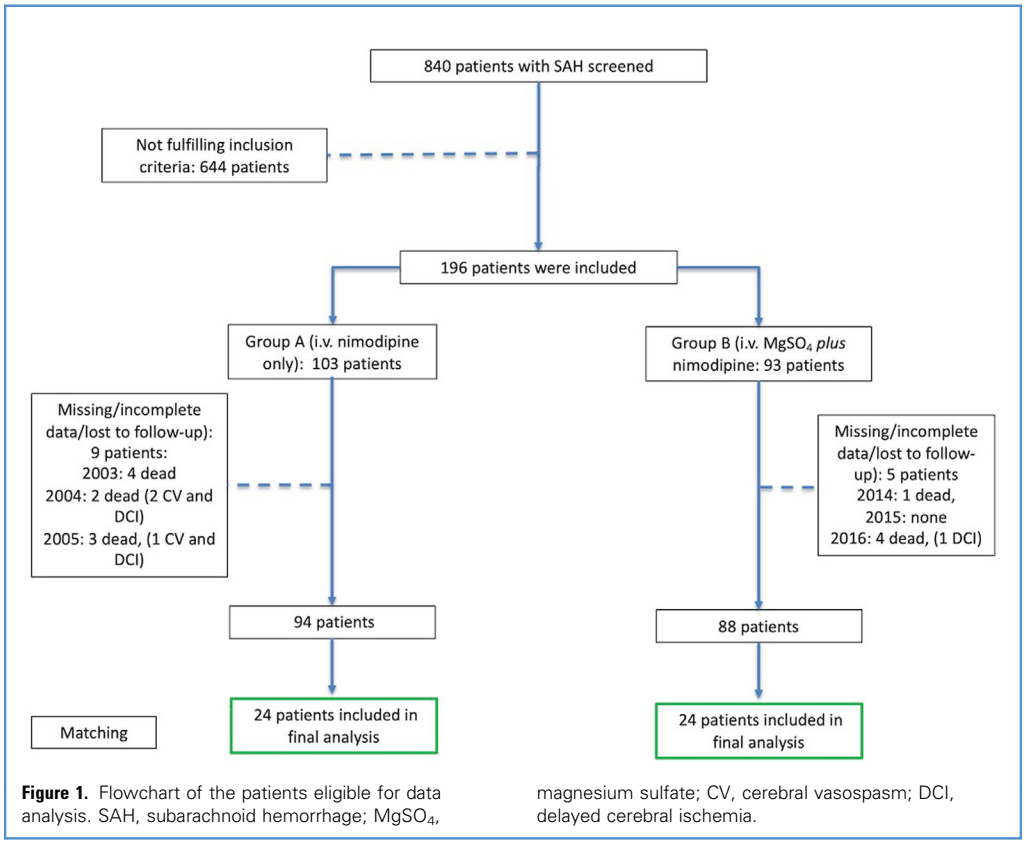

Figure 1. Flowchart of the patients eligible for data analysis. SAH, subarachnoid hemorrhage; $MgSO_4$, magnesium sulfate; CV, cerebral vasospasm; DCI, delayed cerebral ischemia.

Inclusion	Exclusion
• Aneurysmal SAH	• Age <18
• Indication for endovascular or microsurgical treatment	• Occult SAH w/o proof of aneurysm
• Period 2014-2016: pts. received $MgSO_4$ within 24 hrs. after ictus	• Traumatic SAH
• Minimum follow-up 18 mo.	• Pregancy
	• Body weight <50 kgs.
	• Renal disease with glomerular filtration rate <15 mL/min

Figure 2. Eligibility criteria. SAH, subarachnoid hemorrhage; $MgSO_4$, magnesium sulfate.

pressure with a target mean arterial pressure of 65 mm Hg. Thereafter, patients received a continuous application of 81 mmol/24 hours for a maximum of 14 days.

Baseline Characteristics

Independent variables were treatment modality (endovascular, microsurgical), SAH grade according to the World Federation of Neurosurgical Societies (WFNS) (WFNS grades 1–3, good-grade SAH; WFNS grades 4–5, poor-grade SAH) and revisited modified Fisher scale,[22] diabetes, parent vessel of the ruptured aneurysm, aneurysm size, aneurysm lobulation, and CSF shunt dependency. Dependent variables were the incidence of CV and DCI, the functional neurological outcome according to the modified Rankin Scale (mRS) score at 3 months and 12 months of follow-up. mRS scores 0–3 were defined as a favorable mRS outcome.

Definition of CV and DCI

CV was identified by transcranial Doppler/duplex ultrasound following computed tomography (CT) angiography based on the definitions of De Oliveira Manoel et al.[23] or digital subtraction angiography (DSA) according to the criteria of Bradford et al.[24] As a prerequisite, new CT angiography and CT perfusion or DSA was ordered in the event of every new focal or global neurological impairment even if transcranial Doppler showed no signs of CV. DCI was defined as new neurological deficit and imaging correlate (new ischemia on CT or magnetic resonance imaging scan) between 3 and 14 days after SAH ictus according to the criteria of Francoeur and Meyer.[5]

Intensive Care Management

According to protocol of our departments, every patient was admitted to the intensive care unit and monitored for at least 14 days with daily transcranial color-coded Doppler/duplex ultrasound. An increase of >30% or 50 cm/second of blood flow velocity or Lindegaard ratio ≥3 within 24 hours was documented as vasospasm and confirmed with CT angiography or DSA. Moreover, in the case of neurological deterioration, cranial computed tomography, CT angiography with CT perfusion, and/or DSA was performed. Every patient received intravenous nimodipine in a dose of 2 mg/hour as a continuous infusion depending on mean arterial pressure (>80 mm Hg) until day 14 after ictus.

Potential Sources of Bias

Due to changes and further digitalization of the patient administration system of the Departments of Neurosurgery, Neuroradiology, and Anesthesiology, we defined 2 time periods to minimize selection bias. Regarding data completeness and accuracy, we rigorously omitted patients with unprecise documentation to reduce the possibility of information bias. Another source of bias could be the manual computing of the matched pair analysis, as we defined the matching variables and created a new matched pair dataset using our statistics software instead of an algorithm.

Statistical Analysis

Data are presented using mean ± 1 SD where appropriate. For categorical data, counts and percentages are given. Matched pair analysis was performed by case-control matching of the following variables: age, arterial hypertension, smoking, WFNS grade, and Fisher grade. Gaussian distribution of all metric variables was analyzed using a Shapiro-Wilk test, histogram, and investigation of kurtosis and skewness. A Pearson χ^2 test for independence was used to analyze effects of not normally distributed categorial variables (nominal or ordinal scaled) on independent variables. Metric variables that were not normally distributed were investigated by a Mann-Whitney U test. The adjusted odds ratio with 95% confidence interval was given if applicable. A P value < 0.05 was considered statistically significant. Data analysis was performed with IBM SPSS v. 26 (IBM Corp., Armonk, New York, USA).

RESULTS

After screening 840 patients, 196 patients with aSAH were identified. Of those, 103 patients (age 49.8 ± 12.3 years; 70 women) were treated with nimodipine only, and 93 patients (age 55.0 ± 12.4 years; 59 women) received additional $MgSO_4$. Matched pair analysis resulted in 48 patients (age 54.2 ± 8.1 years; 30 women, 18 men) included in the final analysis and allocated to group A ($n = 24$) or group B ($n = 24$) (**Figure 1**). Seven patients (29%) had WFNS grade 4 or 5 aSAH in each group. Baseline characteristics including comorbidities of the patients are presented in **Table 1**. There were no statistically significant differences between the groups regarding the investigated parameters.

Effect of $MgSO_4$

In group B, 8 patients experienced CV and 3 patients experienced DCI compared with 11 ($P = 0.055$) and 10 patients ($P = 0.049$) of group A, respectively. Functional outcomes according to mRS scores after 3 and 12 months of follow-up are depicted in **Figures 3** and **4**. Favorable functional outcome (mRS scores 0–3) tended to be better in the $MgSO_4$ group after 3 months ($P = 0.3$) (**Figure 5**), but was significantly better after 12 months ($P = 0.04$) (**Figure 6**).

DISCUSSION

In this retrospective matched case-control analysis, we found evidence that treatment of patients with aSAH with intravenous $MgSO_4$ within 24 hours after ictus onset was associated with a lower incidence of DCI and better functional neurological

Table 1. Patient Demographics

	Overall (n = 48)	$MgSO_4$ Group (n = 24)	Nimodipine Only (n = 24)	OR (95% CI)	P Value
Sex, female:male	30:18	13:11	17:7	2.06 (0.62–6.76)	0.37*
WFNS grade					
1–3	34 (71)	17 (71)	17 (71)	1.21 (0.36–4.12)	1.00*
4–5	14 (29)	7 (29)	7 (29)		
Revised Fisher grade					
0–2 (low risk)	24 (50)	12 (50)	12 (50)	1.0 (0.32–3.10)	1.00*
3–4 (high risk)	24 (50)	12 (50)	12 (50)		
Treatment				3.21 (0.90–11.46)	0.13*
Clipping	32 (67)	19 (79)	13 (54)		
Endovascular	16 (33)	5 (21)	11 (46)		
Parent vessel	48	24	24		0.09*
ACA	2 (4)	2 (8)	0 (0)		
ACoA	17 (35)	8 (33)	9 (38)		
MCA	12 (25)	9 (38)	3 (13)		
Pericallosal	2 (4)	1 (4)	1 (4)		
ICA	6 (13)	1 (4)	5 (21)		
PCoA	4 (8)	3 (13)	1 (4)		
BA	3 (6)	0 (0)	3 (13)		
PICA	1 (2)	0 (0)	1 (4)		
SCA	1 (2)	0 (0)	1 (4)		
Aneurysm side					1.0*
Right	21 (44)	11 (46)	10 (42)		
Left	11 (23)	5 (21)	6 (25)		
N/A	16 (33)	8 (33)	8 (33)		
Aneurysm size, mean ± SD	6.8 ± 4	6.5 ± 3.3	7 ± 4.7		0.81†
Lobulated	11/48 (23)	5/24 (21)	6/24 (25)	0.79 (0.21–3.05)	1.0*
Diabetes mellitus	6/48 (13)	3/24 (13)	3/24 (13)	1.0 (0.18–5.53)	1.0*
Shunt dependency	12/48 (25)	5/24 (21)	7/24 (29)	0.64 (0.17–2.40)	0.74*

Values are reported as number or number (%) except for aneurysm size, which is reported as mean ± SD.
$MgSO_4$, magnesium sulfate; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies; ACA, anterior cerebral artery; ACoA, anterior communicating artery; MCA, middle cerebral artery; ICA, internal carotid artery; PCoA, posterior communicating artery; BA, basilary artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; N/A, not available.
*Pearson χ^2 test.
†Mann-Whitney U test.

outcome 12 months after treatment. The novelty of this study lies in our observation that timing of $MgSO_4$ may be a critical factor and a possible reason that previous RCTs have failed to demonstrate a clinical benefit.

$MgSO_4$, which physiologically acts as a calcium antagonist, has a proven neuroprotective effect, and its dose-dependent risk profile is well known.[8,9,25] Moreover, patients with aSAH and low serum $MgSO_4$ levels had progression of their accompanying intraparenchymal hemorrhage and a higher risk of rupture of incidental aneurysms.[10,11] A direct comparison between nimodipine and $MgSO_4$ in a prospective RCT revealed an equivalent efficacy of both drugs to prevent delayed ischemic neurological deficits.[26]

However, 3 RCTs could not clearly show the positive benefit of $MgSO_4$ therapy. The MASH trial suggested a reduction of DCI and related poor clinical outcome.[27] However, the IMASH and

MASH-2 trials compared $MgSO_4$ with placebo, and both failed to show a beneficial effect of $MgSO_4$ on the clinical condition.[28,29] There are several possible explanations for the lack of evidence in these pooled studies. First, no magnesium and calcium levels in the CSF were measured, leaving the actual concentrations and the competitive interaction with the vascular Ca^{2+} cell receptors obscure. Second, time from onset of SAH to $MgSO_4$ administration has been >24 hours, and no comparable timing of administration or dosing schedules were applied. Third, the insufficient concentration of $MgSO_4$ in CSF could hamper neuroprotective effects.[17,18] Fourth, the definition and detection of CV and DCI was incongruent throughout the RCTs.

Concerning the timing of $MgSO_4$ application, the Würzburg group recently published their single-institution results of their 12-year experience.[30] According to their protocol, continuous intravenous $MgSO_4$ was given with an initial rate of 8 mmol/hour starting between day 0 and 1 immediately after aneurysm treatment. From a total number of 548 patients, the target serum concentration of ≥2 mmol/L was achieved in 453 patients, and a reduced concentration of 1.1–1.9 mmol/L was achieved in 60 patients, and only 35 patients were treated without $MgSO_4$. The investigators observed higher DCI rates if the minimum target concentration of 2 mmol/L was not achieved. As mentioned before, these authors pointed out the relevance of individual patient factors such as age, weight, kidney function, and blood-brain barrier effect on $MgSO_4$ concentrations in blood and CSF. In our study, those factors were anticipated by our inclusion/exclusion criteria and our matching algorithm.

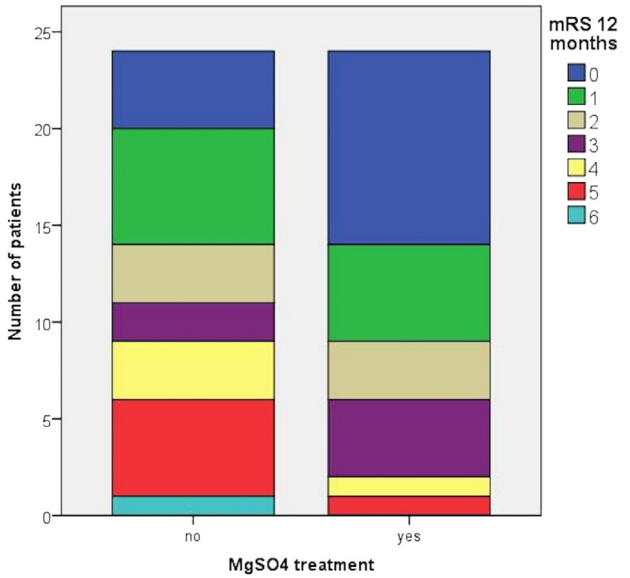

Figure 4. Functional outcome of both treatment groups after 12 months. mRS, modified Rankin Scale; $MgSO_4$, magnesium sulfate.

The perception of the origin of DCI and its pathomechanism has changed throughout the last decade. It was first thought to relate closely to the vasoconstriction of major arteries, and

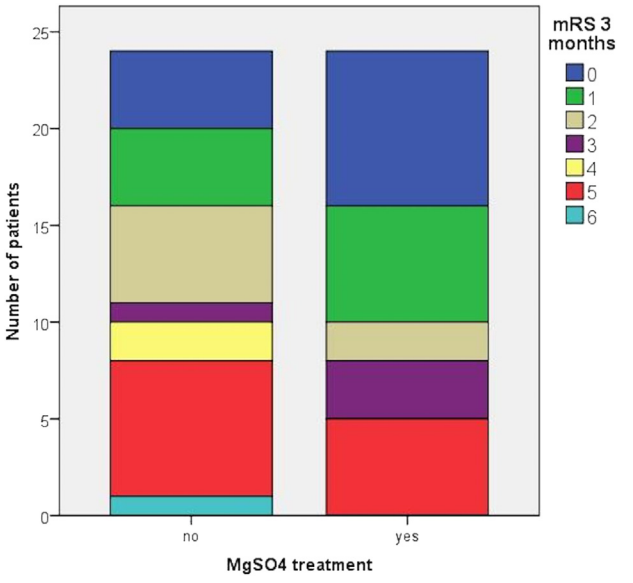

Figure 3. Functional outcome of both treatment groups after 3 months. mRS, modified Rankin Scale; $MgSO_4$, magnesium sulfate.

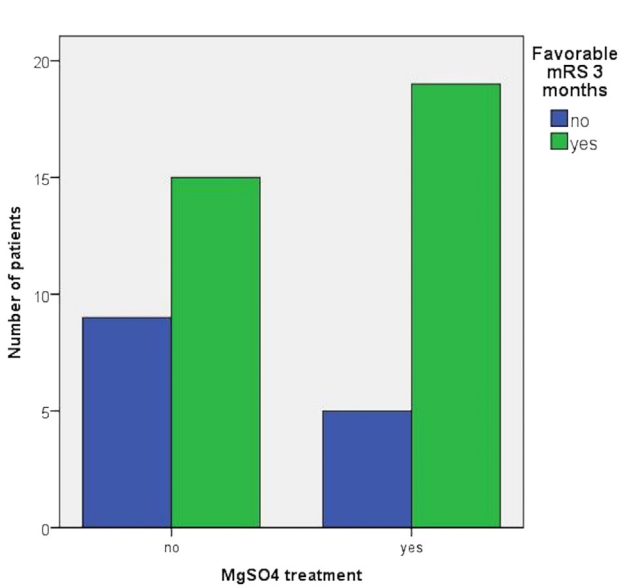

Figure 5. Favorable functional outcome of both treatment groups after 3 months. mRS, modified Rankin Scale; $MgSO_4$, magnesium sulfate.

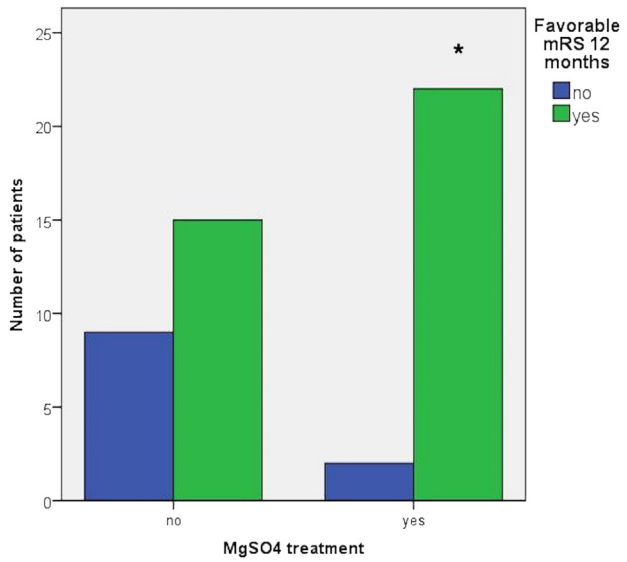

Figure 6. Favorable functional outcome of both treatment groups after 12 months. *$P < 0.05$, Pearson $\chi 2$ test. mRS, modified Rankin Scale; $MgSO_4$, magnesium sulfate.

successful treatment of CV was believed to convert into better functional outcome without relevant cerebral ischemia. CV occurs in up to 70% of all patients with aSAH; however, only 20%–30% develop actual neurological deterioration due to DCI. To our knowledge, the conclusion that could be drawn from current data is that the pathophysiological mechanism of vasospasm and the post-SAH delayed ischemic deficit extends to the level of cerebral microcirculation.[6,23,30] Underlining the proposed changes in microcirculation, cellular function, and metabolism associated with DCI, we conducted a pilot study to examine the impact of aSAH on capillary-venous microcirculation using a noninvasive combined laser Doppler flowmeter and tissue spectrophotometer during surgery.[31,32] We also found that the early application of $MgSO_4$ prevented DCI in these patients.[33]

Regarding the administration of nimodipine, this drug was given intravenously in our department due to its higher bioavailability, stable pharmacokinetics, and better controllability. A recent meta-analysis concluded that intravenous and enteral nimodipine may be equally effective in patients with aSAH, although high-level (level I) evidence is still lacking.[34] This leads to the limitations of our study, as one major confounding factor is the vasodilative effect of nimodipine, which could not be omitted in the $MgSO_4$ group as it is the gold standard therapy for CV. Thus, simultaneous administration of these calcium antagonists could impede the detection of possible neuroprotective mechanisms.

Limitations

By its retrospective nature, our data analysis is prone to potential sources of bias and confounding factors. We report on a single-institution experience that covers 2 different periods 10 years apart. This could be a major flaw and bias toward the possible effect of $MgSO_4$. Over time, diagnostic modalities, hospital structures with high- and low-volume centers, specialized neurocritical care units, aSAH treatment protocols, and intensive care unit therapy itself improved, which has an impact on the time of diagnosis and patient outcome.[35,36] Mixing different therapeutic methods (microsurgical clipping, endovascular treatment) and refinement of endovascular methods has an impact on the incidence of CV and DCI as well.[37] Although CV seems to be more common in patients who underwent microsurgical clipping, the higher portion of surgical cases in our study should have led to a higher occurrence of CV and poorer outcome. Of note, none of the aneurysms in the $MgSO_4$ group B were located in the basilar artery, superior cerebellar artery, or posterior inferior cerebellar artery with a higher percentage of middle cerebral artery aneurysms compared with the nimodipine-only group A. Group A included 4 patients with aneurysms located in the basilar artery, superior cerebellar artery, or posterior inferior cerebellar artery and 3 of those patients underwent surgical clipping. Bleeding source and therapeutic strategy (endovascular vs. clipping) could be a potential confounder regarding functional outcome. However, even with a higher number of 9 patients with middle cerebral artery aneurysms (8 of 9 patients underwent clipping) in group B compared with 3 patients (all patients underwent clipping) in group A, there was no statistical difference of the observed parameters. In our opinion, the results cannot be solely attributed to refined conservative treatment or technical revolution.

Other potential confounders include mean arterial blood pressure during the initial 14 days of therapy, observer-dependent quality of transcranial ultrasound investigations or anesthetic/intensive care regimen. Triple-H therapy, for example, was obsolete in our department since 2012 due to the discovery of severe side effects and adverse events of hydroxyethyl starch solutions in patients with sepsis.

Reasons for the low rate of included patients lie in the matched-pair analysis and the completeness of data. Despite the small number of included patients, it represents a risk-stratified and adjusted sample of aSAH patients that provides a high degree of data comparability. Thus, selection and information bias must be mentioned. Although we tried to reduce selection bias by performing a matched-pair analysis, which included known risk factors of CV and DCI, "matching itself does not control for confounding by the matching factors."[38] Controversially, a bias can be introduced because controls are made more similar for the event itself.

One critical point is the actual drug levels of $MgSO_4$ and calcium in serum and CSF, which were not determined at the same time on a regular basis. As no standard concentration of $MgSO_4$ for this specific indication exists, the chosen dose is based on previous dose-finding studies and published trial protocols.[9,39] Thus, insufficient drug concentrations can influence the effect of $MgSO_4$, which subsequently could diminish any differences in the incidence of CV, DCI, and functional outcome.15,16,17,18Despite these limitations, we are planning to conduct a prospective, multicenter RCT to investigate the effect of $MgSO_4$ under monitoring of CSF and serum concentrations in patients with aSAH in the near future.

CONCLUSIONS

In this retrospective matched case-control analysis study, the incidence of CV and DCI was lower in patients receiving intravenous $MgSO_4$ within 24 hours after onset of aSAH. Only after 12 months, favorable functional outcome was more likely in patients who received $MgSO_4$ compared with nimodipine. The data support the hypothesis of beneficial effects of $MgSO_4$. However, these neuroprotective effects have to be proven by conducting a prospective randomized controlled study that includes quantitative measurement of CV and DCI and is controlled for known risk factors, impacts of calcium and magnesium concentrations in blood and CSF, manipulation (e.g., diversion by ventricular/lumbar drains or ventriculostomy), or pharmacologic impact of anesthetic agents (e.g., venodilation caused by inhalational anesthetics).

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Julian Feulner: Conceptualization, Investigation, Writing — original draft. **Cornelia S. Weidinger:** Data curation, Formal analysis, Writing — review & editing. **Arnd Dörfler:** Supervision. **Torsten Birkholz:** Project administration, Supervision. **Michael Buchfelder:** Supervision, Writing — review & editing. **Björn Sommer:** Data curation, Formal analysis.

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