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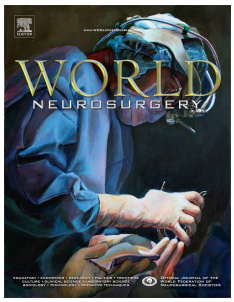

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Early intravenous magnesium sulfate and its impact on cerebral vasospasm as well as delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: A retrospective matched case-control analysis

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ABSTRACT

Introduction: Magnesium sulfate ($MgSO_4$) is a potential neuroprotective agent for patients with aneurysmal subarachnoid hemorrhage (aSAH). We analysed the effect of early application of intraoperative intravenous magnesium sulfate ($MgSO_4$) and compared the rate of cerebral vasospasm (CV), delayed cerebral ischemia (DCI) and neurological outcome in two patient cohorts.

Material and methods: A retrospective matched-pair analysis from patients of a single center in Germany was performed without (group A) and with (group B) $MgSO_4$ application <24 hrs 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, DCI, and neurological outcome using the modified Rankin Scale (mRS) 3 and 12 months after SAH were recorded.

Results: 196 patients fulfilled the inclusion criteria. After risk stratification, 48 patients were included in the final analysis (mean±SD age 54.2±8.1yrs, 30 f, 18 m) and were assigned to group A (n=24) or group B (n=24). CV occurred less frequently in group B (33%) than in A (46%). Likewise, DCI was present in 13% (group B) as compared to 42% (group A). After 12 months, 22 patients of group B had a favorable functional outcome (mRS 0 to 3) compared to 15 of group A.

Conclusions: In this study, the incidence of CV and DCI was lower in patients receiving intravenous $MgSO_4$ within 24 hrs after aneurysmal SAH onset. Favorable functional outcome was more likely in the magnesium 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 in 2010.[1] Being a life-threatening disease of the central nervous system, it affects people at the age of 40 to 60 years in approximately 60% of all SAH cases. Despite best medical care, the in-hospital mortality is reported with 18% to 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 and leading to neurological deterioration in up to 30% of the 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 aneurysmal SAH patients and raises the risk of CV and DCI.[9] Patients suffering from hypomagnesemia had higher aneurysmal rupture rates and in SAH-patients more extensive intracerebral hemorrhage was diagnosed.[10-12] Thus, recommendations advise to prevent hypomagnesemia in these patients.[13]

However, several randomized-controlled trials have not verified the clinical benefit of $MgSO_4$ therapy in patients with aneurysmatic SAH regarding functional neurological outcome yet, 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.[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 magnesium sulfate. Furthermore, we intended to investigate the impact of $MgSO_4$ on functional neurological status.

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, two different time periods (2003-2005, 2014-2016) were observed and a total of 840 patients were screened using digital patient charts (Figure 1). Eligibility criteria are given in Figure 2. Matching criteria included the known risk factors that are associated with CV (smoking, 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, Germany (approval no. 377_16 Bc) and with the 1964 Helsinki declaration and its amendments. The 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 (i.v.) nimodipine with a starting dose of 1mg/h to a maximum of 2 mg/h, depending on the hypotensive reaction. Due to paradigm changes based on the available scientific data available at that time, early i.v. administration of $MgSO_4$ was routinely established over the years. The period between 2014 and 2016 was chosen due to a change in the PACS and PAS systems of the departments (Anesthesiology, Neuroradiology, 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 $MgSO_4$ sulfate 10% application with a loading dose of 50 mg/kg body weight over 1 hour. The infusion rate (20-40 mmol) depended on blood pressure with a target MAP of 65 mm Hg. Thereafter, patients received a continuous application of 81 mmol/24h for a maximum of 14 days.

Baseline characteristics

Independent variables were treatment modality (endovascular, microsurgical), SAH grade according to WFNS (good SAH: WFNS 1-3, poor SAH: WFNS 4-5) 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) at 3 and 12 months of follow-up. Scores mRS 0 to 3 were defined as “favorable mRS outcome”.

Definition of CV and DCI

Cerebral vasospasm (CV) was identified by transcranial Doppler/Duplex ultrasound following CT-angiography based on the definitions of De Oliveira Manoel and co-workers[23] or digital subtraction angiography (DSA) according to the criteria of Bradford and co-workers[24]. As a prerequisite, every new focal or global neurological impairment triggered CT angiography and CT perfusion or DSA even if TCD showed no signs of CV. Delayed cerebral ischemia (DCI)

was defined as new neurological deficit and imaging correlate (new ischemia in CT or MRI scan) between day 3 and 14 after SAH ictus according to the criteria of Franceur and Meyer.[5]

Intensive care management

According to our departments' protocol 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 more than 30% or 50 cm/s of blood flow velocity or Lindegaard ratio ≥3 within 24 hours was documented as vasospasm and confirmed with CTA or DSA. Moreover, in the case of neurological deterioration, CCT, CTA with CT perfusion and/or DSA was performed. Every patient received i.v. nimodipine in a dose of 2 mg/h as a continuous infusion depending on MAP (>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 Department of Neurosurgery, Neuroradiology and Anesthesiology, we defined two 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 the manually computing of the matched pair analysis, as we defined the matching variables and created a new matched pair data set using our statistics software instead of an algorithm.

Statistical analysis

Data are presented using mean and one standard deviation (SD) where appropriate. For categorical data, counts and percentages are given. Matched pair analysis was performed by case-control matching of the variables age, arterial hypertension, smoking, WFNS grade and Fisher grade. Gaussean distribution of all metric variables was analysed using a Shapiro-Wilk test, histogram, and investigation of kurtosis and skewness. A Pearson´s chi-square test for independence was used to analyse 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 (OR) with 95% confidence intervals (95%CI) were given if applicable. A p-value of <.05 was considered statistically significant. Data analysis was performed with IBM SPSS v. 26 (IBM Corp, Armonk, United States).

RESULTS

After screening 840 patients, 196 patients with aSAH were identified. Of those, 103 patients (70 females, age 49.8±12.3 yrs) were treated with nimodipine only, 93 (59 females, 55.0±12.4 yrs) received additional $MgSO_4$. Matched pair analysis resulted in 48 patients (mean±SD age 54.2±8.1yrs, 30 f, 18 m) who were included in the final analysis and allocated to group A (n=24) and B (n=24, Fig.1). Seven patients (29%) suffered from aSAH WFNS grade 4 or 5 in each group. Baseline characteristics including co-morbidities of these patients are presented in Table 1. There were no statistically significant differences regarding the investigated parameters between both groups.

Effect of $MgSO_4$

In group B, eight patients suffered from CV and three patients from DCI compared to 11 (p=0.055) and 10 patients (p= 0.049) of group A, respectively. Functional outcome according to modified Rankin scale after 3 and 12 months are depicted in figures 3 and 4. Favorable functional outcome (mRS 0 to 3) tended to be better in the $MgSO_4$ group after 3 months (p=0.3, Fig. 5) but was significantly better after 12 months of follow-up (p=0.04, Fig. 6).

DISCUSSION

In this retrospective matched case-control analysis, we found evidence that treatment of aSAH patients with i.v. $MgSO_4$ within 24 hours after ictus onset was associated with a lower incidence of DCI and better functional neurological 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 randomized-controlled trials have failed to demonstrate a clinical benefit.

Magnesium, 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 aneurysmal SAH and low serum magnesium levels had a progress of their accompanying intraparenchymal hemorrhage and a higher risk of rupture of incidental aneurysms.[10,11] A direct comparison between nimodipine and magnesium sulfate in a prospective RCT reveals an equivalent efficacy of both drugs to prevent delayed ischemic neurological deficits.[26] Unfortunately, three randomized controlled trials could not clearly show the positive benefit of magnesium therapy. The MASH trial suggested a reduction of delayed cerebral ischemia and

related poor clinical outcome.[27] However, the IMASH and MASH-2 trials compared magnesium sulfate with placebo and both failed to show a beneficial effect of magnesium 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 magnesium administration has been >24 hours, and no comparable timing of administration or dosing schedules were applied. *Third*, the insufficient concentration of magnesium in cerebrospinal fluid (CSF) could hamper neuroprotective effects.[17,18] *Fourth*, the definition and detection of cerebral vasospasm and delayed cerebral ischemia 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 i.v. magnesium sulfate was given with an initial rate of 8 mmol/h 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, a reduced concentration between 1.1 – 1.9 mmol/l in 60 patients and only 35 patients were treated without $MgSO_4$. They observed higher DCI rates if the minimum target concentration of 2 mmol/l was not achieved. As mentioned before, Wipplinger and Co-workers pointed out the relevance of individual patient factors such as age, weight, kidney function as well as the blood brain barrier effect on magnesium concentrations in blood and CSF. In our study, those factors were anticipated by our inclusion/exclusion criteria and our matching algorithm.

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

successful treatment of CV was believed to convert into better functional outcome without relevant cerebral ischemia. Cerebral vasospasm occurs in up to 70% of all aneurysmal SAH patients, 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 non-invasive 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 vasodilatative effect of nimodipine, which could not be omitted in the $MgSO_4$ group as it is the "gold" standard therapy for CV. Thus, a 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 two different periods each 10 years apart. This could be a major flaw and bias towards 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] Despite 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 BA, SCA or PICA with a higher percentage of MCA aneurysms as compared to the nimodipine only group A. Group A included 4 patients with aneurysms located in BA, SCA or PICA, and 3 patients of those 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 MCA aneurysms (8/9 patients underwent clipping) in group B compared to 3 (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 since controls are made more similar for the event itself.

One critical point is the actual drug levels of magnesium 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 exist, 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.[15-18]

Despite these limitations, we are planning to conduct a prospective, multicenter randomized controlled trial to investigate the effect of $MgSO_4$ under monitoring of CSF and serum concentrations in aSAH patients 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 hrs after aneurysmal SAH onset. Only after 12 months, favorable functional outcome was more likely in patients who received magnesium compared to nimodipine. The data supports the hypothesis of beneficial effects of magnesium. However, these neuroprotective effects have to be proven by conducting a

prospective randomized controlled study that includes quantitative measurement of CV and DCI, is controlled for known risk factors, impacts calcium and magnesium concentrations in blood and CSF, manipulation (e.g. diversion by ventricle/lumbar drains or ventriculostomy), or pharmacologic impact of anesthetic agents (eg. venodilation caused by inhalational anesthetics).

Declarations

Ethical Approval

The research conducted has been performed in accordance with the Declaration of Helsinki. The responsible local ethics committee of the Friedrich-Alexander University Erlangen-Nuremberg, Germany had no ethical concerns (approval no. 377_16 Bc).

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions

All authors (JF, CSW, AD, TB, MB, BS) contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JF, CSW, and BS. The first draft of the manuscript was written by BS, and all authors commented on previous versions of the manuscript. All authors (JF, CSW, AD, TB, MB, BS) read and approved the final manuscript. BS has given final approval of the version to be published. BS agreed to be

accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

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

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Conflict of interests

The authors declare no conflict of interests.

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FIGURE LEGENDS

Figure 1. Flow chart of the patients eligible for data analysis.

Figure 2. Eligibility criteria.

Figure 3. Functional outcome of both treatment groups after 3 months.

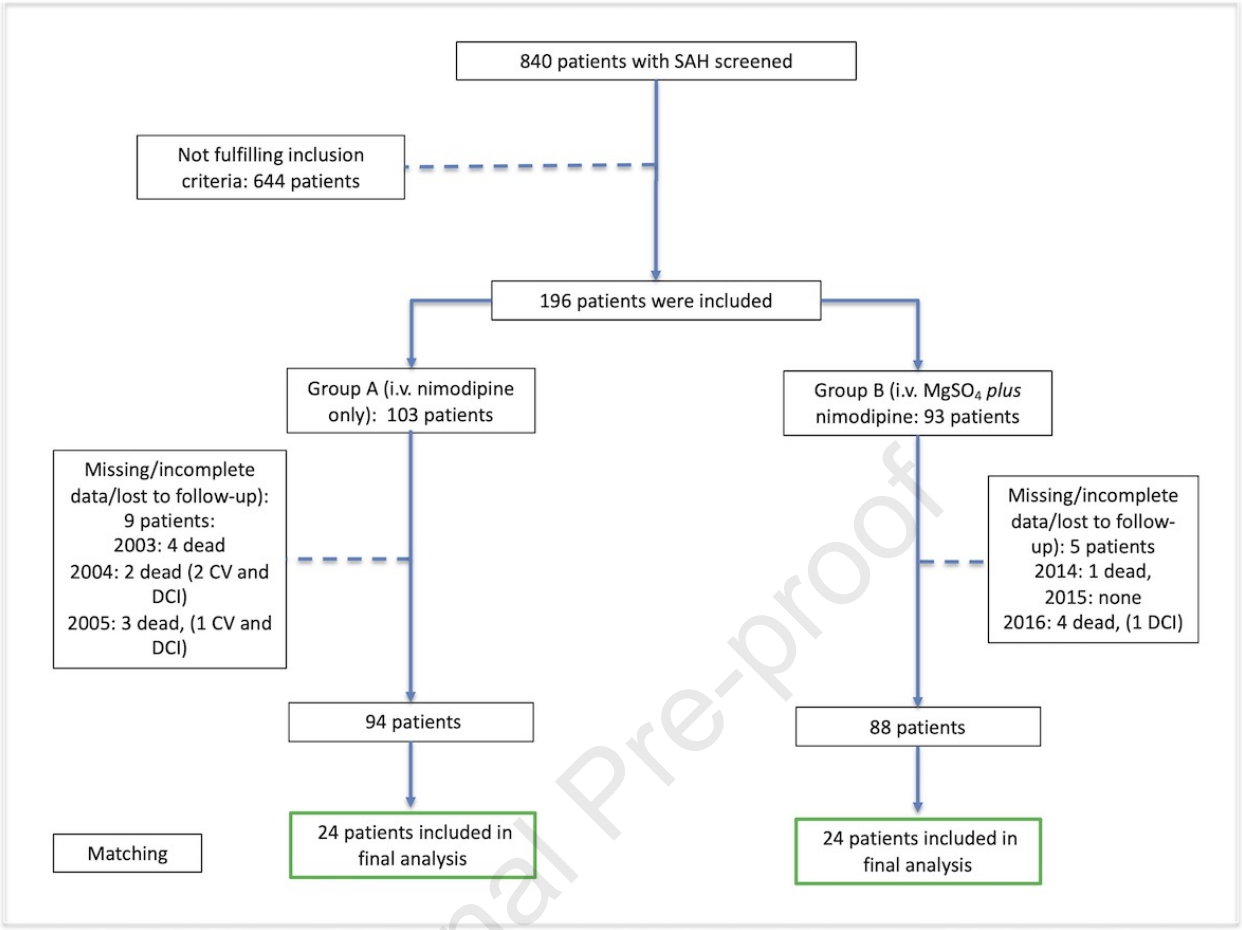
Figure 4. Functional outcome of both treatment groups after 12 months.

Figure 5. Favorable functional outcome of both treatment groups after 3 months.

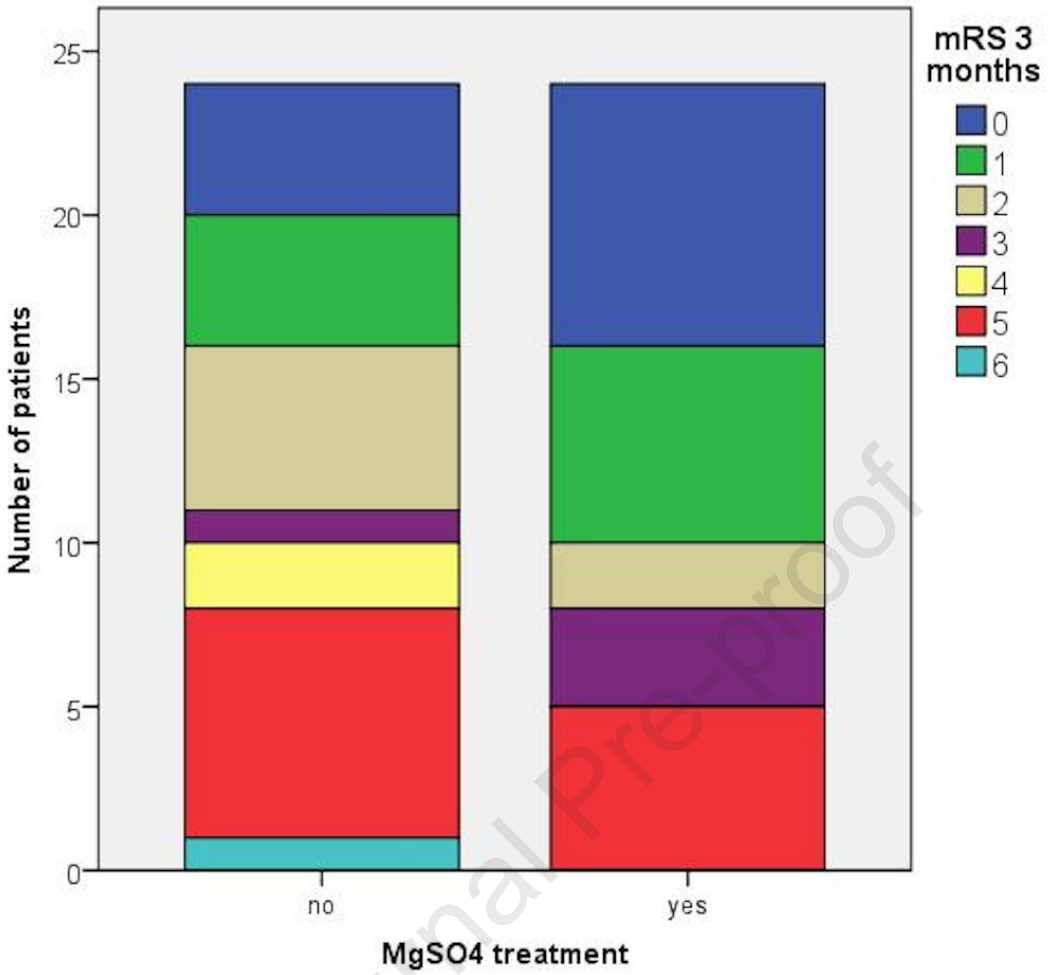
Figure 6. Favorable functional outcome of both treatment groups after 12 months. *$p<0.05$, Pearson´s chi-squared test.

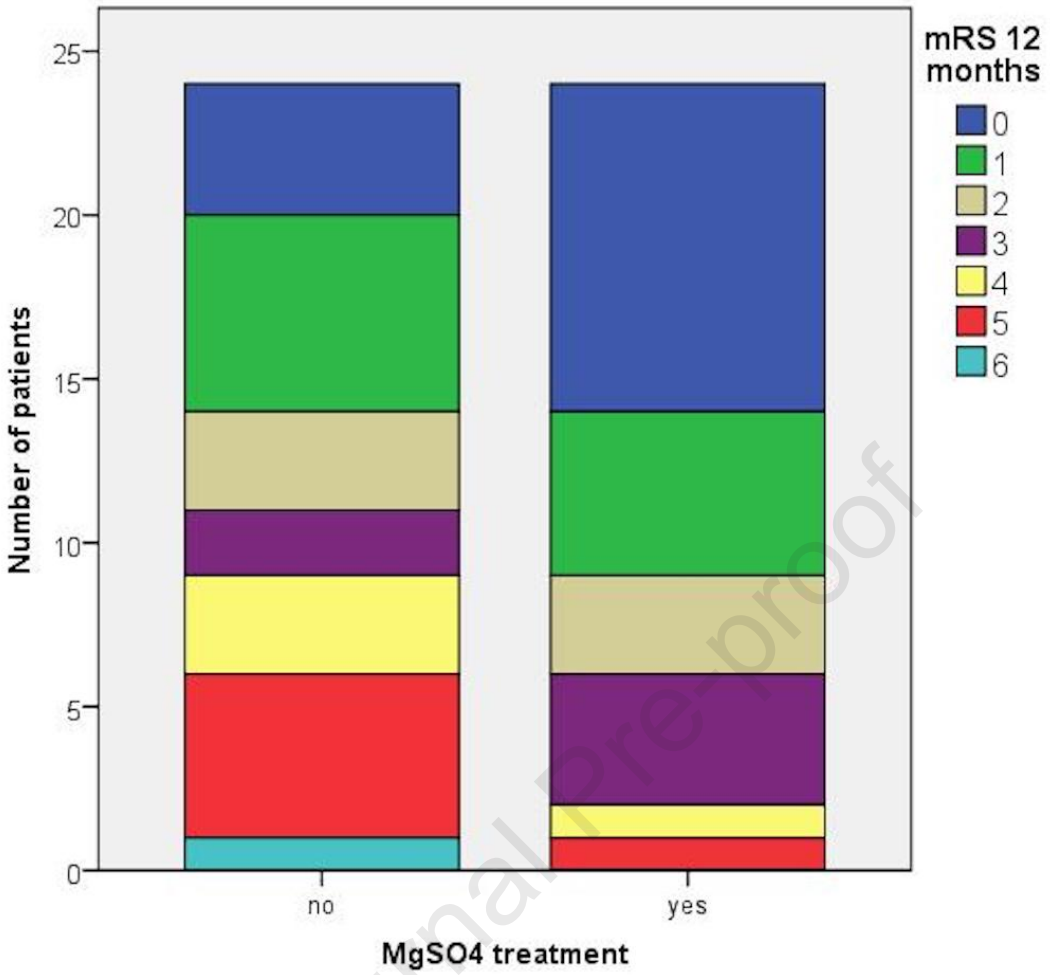
Table 1. Patient demographics. Metric values given in mean±1 standard deviation. ACA: anterior cerebral artery, AcoA: anterior communicating artery, MCA: middle cerebral artery, ICA: internal carotid artery, PcoA: posterior communicating artery, BA: basilary artery, PICA: posterior inferior cerebellar artery, SCA: superior cerebellar artery. OR: odds ratio, CI: confidence interval. §: Pearsons chi-squared test, ◊: Mann-Whitney-U test

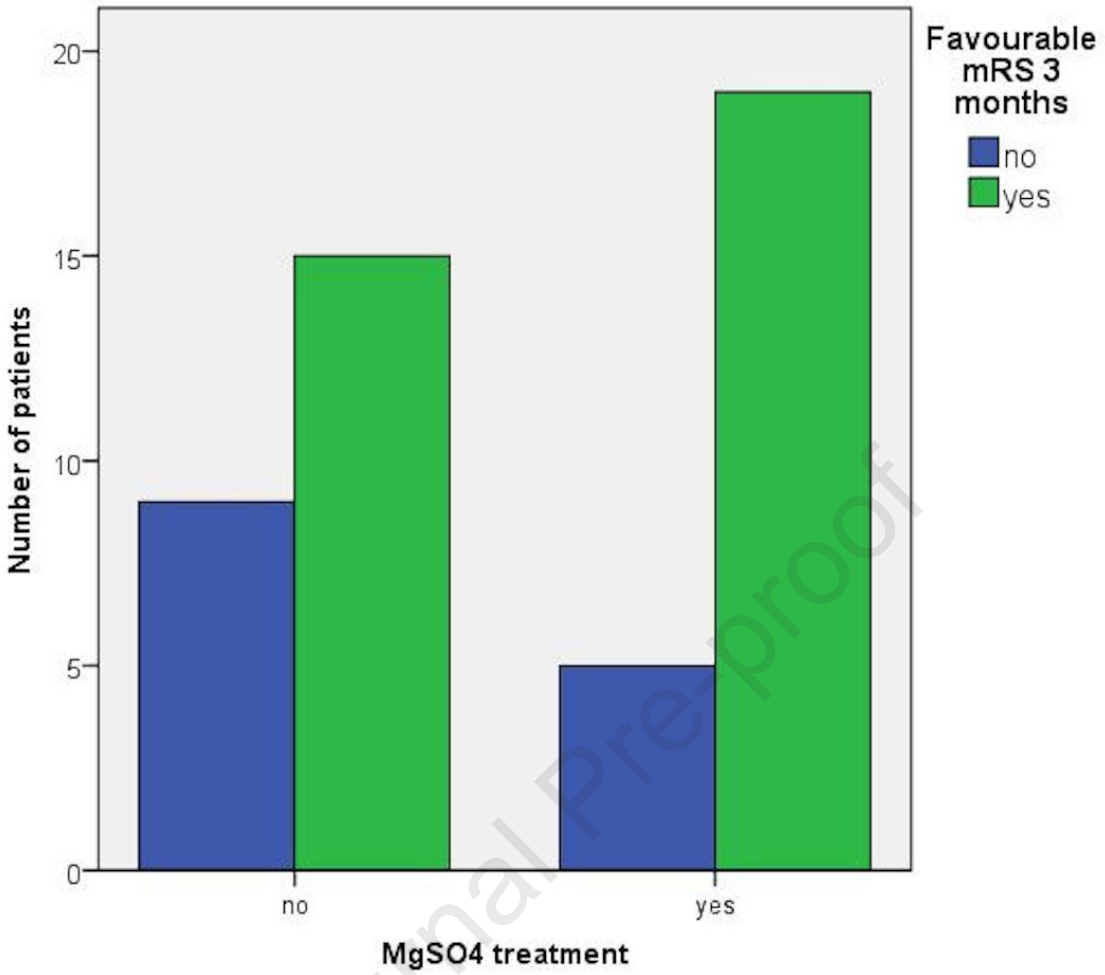
	overall (n=48)	MgSO4 group (n=24)	Nimodipine only (n=24)	OR (95% CI)	p Value
Gender (f:m)	30:18	13:11	17:7	**2.06 (.62 to 6.76)**	0.37§
WFNS grade 1-3, n (%)	34 (71)	17 (71)	17 (71)	**1.21 (.36 to 4.12)**	1.00§
WFNS grade 4-5, n (%)	14 (29)	7 (29)	7 (29)		
Rev. Fisher grade 0-2 (low risk), n (%)	24 (50)	12 (50)	12 (50)	**1.0 (.32 to 3.10)**	1.00§
Rev. Fisher grade 3-4 (high risk), n (%)	24 (50)	12 (50)	12 (50)		
Treatment, n (%)				**3.21 (.90 to 11.46)**	0.13§
Clipping	32 (67)	19 (79)	13 (54)		
Endovascular	16 (33)	5 (21)	11 (46)		
Parent vessle, n (%)	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)		
Pericallosa	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, n (%)					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	6.8±4	6.5±3.3	7±4.7		0.81◊
Lobulated	11/48 (23)	5/24 (21)	6/24 (25)	**.79 (.21 to 3.05)**	1.0§
Diabetes mellitus	6/48 (13)	3/24 (13)	3/24 (13)	**1.0 (.18 to 5.53)**	1.0§
Shunt dependency	12/48 (25)	5/24 (21)	7/24 (29)	**.64 (.17 to 2.40)**	0.74§

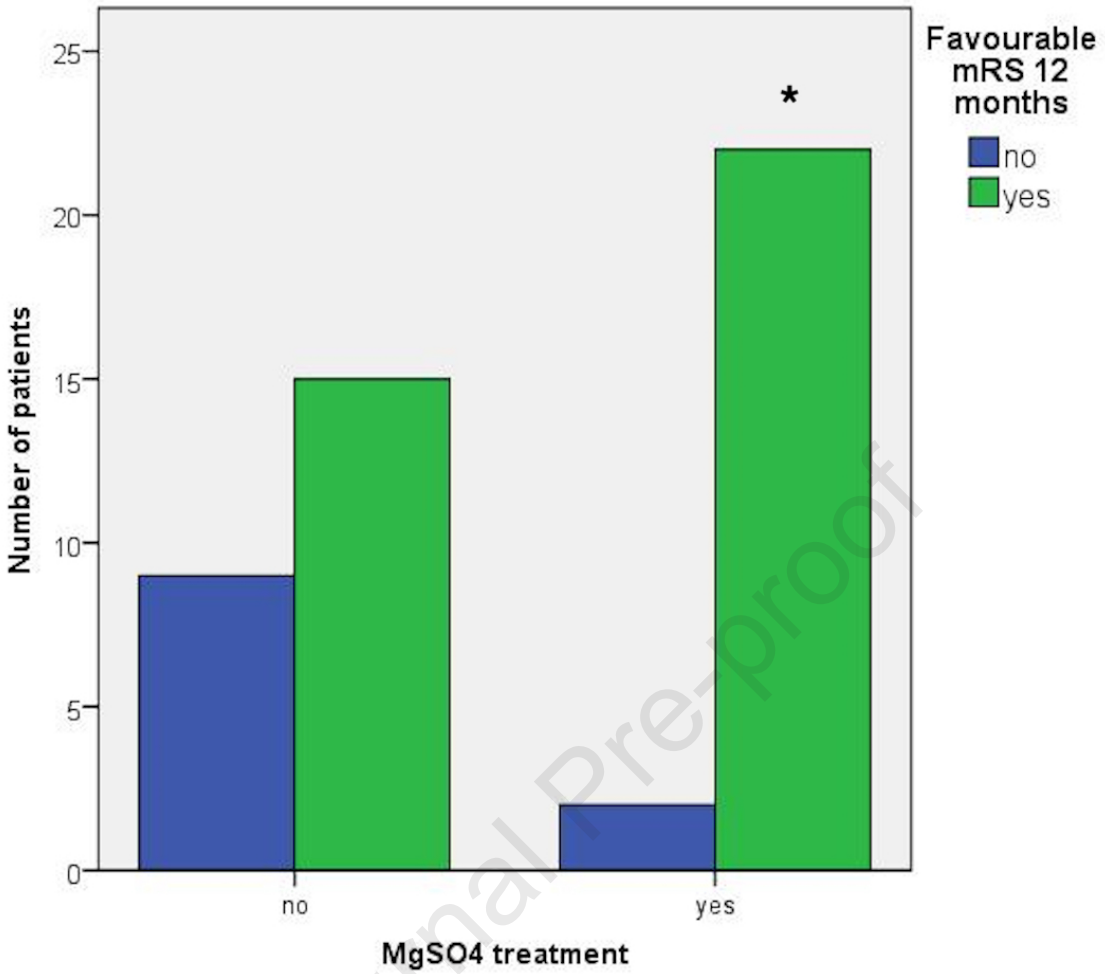


Inclusion	Exclusion
• Aneurysmal SAH	• Age <18
• Indication for endovascular or microsurgical treatment	• Occult SAH w/o proof of aneurysm
• Period 2014-2016: pts. received $MgSO_4$ within 24 hrs. after ictus	• Traumatic SAH
• Minimum follow-up 18 mo.	• Pregancy
	• Body weight <50 kgs.
	• Renal disease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









Abbreviation list

ACA: anterior cerebral artery, AcoA: anterior communicating artery, CI: confidence interval, CV: cerebral vasospasm, CGT: computed tomography, DCI: delayed cerebral ischemia, DSA: digital subtraction angiography, ICA: internal carotid artery, ICU: intensive care unit, MAP: mean arterial pressure, MCA: middle cerebral artery, $MgSO_4$: magnesium sulfate, MRI: magnetic resonance imaging, mRS: modified Rankin scale, OR: odds ratio, PcoA: posterior communicating artery, BA: basilary artery, PACS: picture archiving and communication system, PAS: patient administration system, PICA: posterior inferior cerebellar artery, aSAH: aneurysmal subarachnoid hemorrhage, SCA: superior cerebellar artery, SD: standard deviation, WFNS: World Federation of Neurosurgical Societies

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: