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MAGNESIUM PROTECTS IN EPISODES OF CRITICAL PERFUSION AFTER ANEURYSMAL SAH

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Abstract

Background: To analyze whether magnesium has a neuroprotective effect during episodes that indicate a critical brain perfusion after aneurysmal subarachnoid hemorrhage (SAH).

Methods: 107 patients with aSAH were randomized to continuously receive intravenous magnesium sulfate with target serum levels of 2.0 – 2.5 mmol/l (n = 54) or isotonic saline (n = 53). Neurological examination and transcranial Doppler sonography (TCD) were performed daily, Perfusion-CT (PCT) was acquired in 3-day intervals, angiography in case of suspected vasospasm. The primary endpoint was the development of secondary infarction following episodes of delayed ischemic neurological deficit (DIND), elevated mean flow velocity (MFV) in TCD or pathological findings in PCT.

Results: In the magnesium group, 9 episodes of DIND were registered, none was followed by secondary infarction. In the control group, 23 episodes of DIND were registered, 9 were followed by secondary infarction ($p < 0.05$). In the magnesium group, 114 TCD-measurements showed an elevated MFV(> 140 cm/s). 7 were followed by new infarction. In control patients, 135 measurements showed elevated MFV, 32 were followed by new infarction ($p < 0.05$). 10 of 117 abnormal PCT-findings were followed by new infarction, compared to 30 of 122 in the control-group ($p < 0.05$).

Conclusion: DIND, elevated MFV in TCD and abnormal PCT are findings which are associated with an increased risk to develop delayed secondary infarction. The results of this analysis suggest that magnesium-treatment may reduce the risk to develop infarction in a state of critical brain perfusion.

Keywords

• subarachnoid hemorrhage • magnesium • neuroprotection • delayed cerebral infarction

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Introduction

The data on beneficial effects of magnesium-treatment in patients who suffered aneurysmal subarachnoid hemorrhage (SAH) is conflicting. Experimental results in cerebral ischemia [1-4] and early clinical data in stroke patients [5, 6] supported the idea that magnesium may act as a neuroprotective agent in cerebral ischemia and SAH. In the last two decades, several clinical studies have shown beneficial effects of magnesium in SAH [7-14]. However, two large multicenter trials failed to confirm a reduced incidence of delayed cerebral ischemia and an improvement of clinical recovery by intravenous administration of magnesium sulfate [15, 16] and caused some disillusionment. However, the results of these two large studies may have been influenced by the co-medication. In both trials nimodipine was co-administered as a standard medication to magnesium-treated patients as well as to patients of the control-groups. Similar to nimodipine, magnesium predominantly acts as a calcium antagonist. This co-treatment resembles a combination therapy consisting of two similarly acting substances which is, from a pharmacological point of view, unlikely to exert synergistic effects. From the database of a clinical trial, which we previously reported on [14], we conducted this analysis focusing on the potential neuroprotective effects of continuous high-dose administration of magnesium sulfate during episodes of neurological deterioration, arterial vessel narrowing, or abnormalities in perfusion imaging suggesting a critical brain perfusion.

Materials and Methods

The study was approved by the local ethics committee. Informed consent was obtained from the patient or from a permanent or temporary legal guardian. This is a post-hoc analysis from a randomized clinical trial comparing the effects of intravenous magnesium sulfate versus control in patients after aneurysmal SAH [14]. For this purpose, critical events in terms of delayed ischemic neurological deterioration (DIND), angiographic delayed vasospasm, abnormal findings in Perfusion-CT (PCT) and elevated mean flow velocities (MFV) in transcranial Doppler sonography (TCD) were analyzed. While a patient-based analysis has been published previously [14], this is an event-based analysis investigating whether patients in the

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magnesium or control group, respectively, developed secondary infarction after these episodes of critical brain perfusion or not.

Inclusion- and exclusion-criteria

Patients were included if they had suffered aneurysmal SAH within 96 hours before admission and no history of prior bleeding. In- and exclusion criteria have previously been described in detail [14]. All patients were admitted to the neurosurgical intensive care unit of a university hospital. All patients underwent early digital subtraction angiography (DSA) and early endovascular coiling or microsurgical clipping of the ruptured aneurysm within 48 hours after SAH.

Standard management

Clinical assessment included the Glasgow Coma Scale (GCS) score, World Federation of Neurological Societies (WFNS) score and the Hunt/Hess score. Patients were intubated and mechanically ventilated if their GCS score was below 9 points. An external ventricular drainage was implanted if there were signs of hydrocephalus in CT-scans. Care was taken that mean arterial blood pressure did not fall below 80 mmHg in order to prevent episodes of hypotension. Substances used included Ringer's solution, albumin and hydroxyethyl starch (HES 6%) and catecholamines [17]. In case of delayed ischemic neurological deterioration (DIND), elevated mean flow velocities (MFV) in transcranial Doppler sonography (TCD) or signs of perfusion deficits in Perfusion-CT (PCT) maps, patients received hyperdynamic therapy with an optimization of hematocrit (30 – 35%), central venous pressure (10 – 12 mmHg) and induced hypertension.

Randomization and Magnesium dosage

Patients included into the study were randomized to either receive intravenous magnesium sulfate or serve as controls after SAH was diagnosed by CT or lumbar puncture and an aneurysm was demonstrated either by digital subtraction angiography (DSA) or CT-Angiography (CTA). The latest time of occlusion was 96 hours after SAH. In the magnesium group, a loading dose of 16 mmol $MgSO_4$ over half an hour was administered and followed by a continuous infusion of 8 mmol/h. In the following days, the infusion speed was adjusted according to magnesium serum levels in order to keep the latter at 2.0 – 2.5 mmol/l. In the control group, an equal volume of saline was administered. Intravenous magnesium was discontinued at day 10 if there were no signs of clinical deterioration or ultrasonographic vasospasm as measured by TCD and if PCT maps did not show any abnormal patterns. In case of clinical vasospasm, elevated MFV in TCD (over 140 cm/s) or abnormal PCT maps, intravenous magnesium was continued until these findings had normalized. Independent of the study procedures, patients were dismissed or transferred to rehabilitation units if their clinical condition was stable and no more danger for secondary ischemic deterioration was believed to be present.

Assessment of study parameters:

Neurological assessment was conducted three times a day following a standard examination protocol including the GCS, deficits of awareness (person, place, time, situation) and cranial nerves, motor, sensory and coordination deficits of the upper and lower extremities, visual field defects, and speech abnormalities. DIND was defined as a secondary neurological deterioration in the absence of another cause.

A TCD examination was conducted once a day and included the middle and anterior cerebral arteries and internal carotid artery (MCA, ACA, ICA) and the basilar artery. "Ultrasonographic vasospasm" was defined as a MFV >140 cm/s in the anterior circulation and > 90 cm/s in the basilar artery.

A two-slice PCT was obtained after native CT in 3-day intervals (Somatom Plus 4 Volume Zoom, Siemens, Erlangen, Germany) For PCT analysis, a commercially available software was used (Perfusion CT, Siemens). Color maps were visually assessed for side asymmetries or clear bilateral defects indicating a decrease in Cerebral Blood Flow (CBF) or Cerebral Blood Volume (CBV), or an increase in Time-To-Peak (TTP) [18]. All study parameters were assessed by personnel not aware of the patient's study allocation.

In case DIND, elevated MFV in TCD or new deficits in PCT, patients received DSA. Angiographic vasospasm was defined as a reduction of the vessel diameter of more than 50%. In this case, the spasm was treated endovascularly by a balloon catheter or – if not accessible - by a local infusion of nimodipine in a dose of 2 – 4 mg/h for 30 – 60 minutes.

Target parameters

The target parameter was secondary infarction on native CT within the following three days after episodes that suggest critical brain perfusion:

1. An episode of DIND,
2. Angiographic vasospasm,
3. Elevated flow velocities in TCD (MFV > 140 cm/s) and
4. Pathological findings in PCT.

CT-scans were analyzed for new hypodensities. Secondary infarction on plain CT-scans were defined as described by von Kummer et al. [19].

Data analysis

A Fisher exact test was used to analyze incidences. An ROC analysis was performed for trancranial Doppler values to determine the cut-off limit for the value "ultrasonographic vasospasm". This analysis confirmed the inflection point of the ROC curve to be at 140 cm/s. Statistical analysis was performed using GraphPad Prism 4 Statistical Software (GraphPad Software, San Diego, CA). Differences were considered significant at $p < 0.05$. Values are given as mean ± standard deviation for parametric data. For non-parametric data, median values (and mean values) are given.

Results

Patient characteristics

107 patients were included in the study (66 female, 41 male). 54 patients were assigned to receive magnesium, 53 to the control group. The mean age was 50 ± 12 years in the magnesium group and 52 ± 13 years in the control group ($p = 0.15$). The median WFNS score was 3 (mean 2.63 ± 1.61) in the magnesium group and 2 (mean 2.46 ± 1.64) in the control group. The median Hunt/Hess Score was 3 in both groups (mean 2.88 ± 1.24 in the magnesium group and

2.66 ± 1.30 in the control group). The median Fisher Score was 3 in both groups. Patients in the magnesium group were hospitalized 21,9 ± 7.8 days, patients in the control group were hospitalized 20.1 ± 8.2 days. Neurological outcome was assessed by the GOS score after 6 months. The median GOS score was 5 (mean 3.92 ± 1.34) in the magnesium group and 4 (mean 3.45 ± 1.46) in the control group.

Side effects

Potential side effects of parenteral magnesium treatment are electrocardiographic changes, particularly bradycardic arrhythmias and a newly appearing atrioventricular block, hypocalcemic tetany and arterial hypotension. We found a tendency towards a slightly lower heart rate in magnesium-treated patients, several cases with facial flushing and one case with hypocalcemic tetany at serum levels above the target range which was successfully treated by dose-reduction. No further relevant side effects were observed, especially no life-threatening bradycardia and no hemodynamically relevant hypotension. In no case, therapy had to be stopped due to side effects of magnesium sulfate.

Acquisition of Target Parameters

In the entire patient collective, 613 native CT-scans were obtained between admission and discharge. Of these, 484 were obtained at day three after admission or later. Following the study protocol, 414 PCTs were performed. 89 invasive angiographies (DSA) were performed due to suspected vasospasm in 53 of 107 patients. (Table 1)

Neurological assessment

61 of 107 patients (32 in the magnesium group, 29 in the control group) were amenable to neurological assessment throughout the hospital stay except for episodes in which they needed anesthesia or sedation (surgery, endovascular aneurysm treatment, re-angiography for suspected vasospasm) In magnesium-treated patients, 9 episodes of DIND were registered. None was followed by secondary infarction within the following 3 days. In the control-group, 23 episodes of DIND were found. 9 were followed by secondary infarction (p = 0.31).

Angiography

Over all, 89 DSA were performed in 53 patients due to suspected vasospasm. In 27 patients, DSA was conducted more than once (Table 1). 40 digital subtraction angiographies (DSA) were performed in the magnesium group due to suspected vasospasm. 26 showed relevant arterial narrowing, 25 were treated by angioplasty, one by a local intraarterial nimodipine infusion. 2 of 26 were followed by secondary infarction within the following 3 days. In the control-group, 49 DSA were performed, 32 showed relevant arterial vasospasm, 27 were treated by angioplasty, 5 by intraarterial nimodipine infusion. 17 of 32 developed secondary infarction (p = 0.007).

Transcranial Doppler Sonography (TCD)

In the magnesium group, 114 TCD measurements showed elevated MFV. Of those, 7 were followed by secondary infarction. In the control-group, 135 TCD-measurements showed elevated MFV, 32 were followed by secondary infarction (p = 0.0009).

Perfusion-CT (PCT)

In all but 2 cases, Flow-Perfusion maps and Blood Volume maps showed defects which correlated with already demarcated infarction in native CT. In the magnesium group, 117 Time-To-Peak (TTP) maps showed abnormal findings. 10 of those were followed by secondary infarction within the following 3 days. In the control-group, 122 TTP maps showed pathological findings. 30 of those were followed by secondary infarction within the following 3 days (p = 0.006). If differentiated by days after SAH, the differences in occurrence of DIND, ultrasonographic vasospasm and PCT were not statistically significant due to the limited number of patients and events for each respective day.

Discussion

The data of the present analysis show that continuous intravenous treatment with magnesium sulfate significantly reduces the risk to develop secondary cerebral infarction in case of angiographic vasospasm, elevated flow velocities in TCD and pathological findings in PCT. Even in case of DIND, the risk of eventual infarction was reduced.

Promising results in experimental studies have raised high expectations that magnesium might be a valuable drug for the treatment of ischemic diseases of the brain, most of all in stroke patients. Several groups investigated

Table 1: Incidence of vasospasm and secondary infarction Incidence of vasospasm as determined by clinical examination (DIND), angiography (narrowing of vessel diameter > 50 %), TCD (MFV > 140 cm/s), and PCT (asymmetry or clear bilateral deficit). The incidence of DIND was reduced in magnesium-treated patients (32/54 patients in the magnesium group and 29/53 patients in the control group were neurologically assessable through the largest part of their hospital stay). There was no risk-reduction to develop arterial narrowing (DSA, TCD) or pathological perfusion patterns in PCT by magnesium-treatment. The risk to develop secondary infarction, however, was markedly reduced in magnesium-treated patients in conditions of arterial narrowing (DSA, TCD) and pathological findings in PCT. (Fisher Exact Test, DIND = delayed ischemic neurological deficit, DSA = digital subtraction angiography, TCD = transcranial Doppler sonography, PCT = perfusion-CT, $MgSO_4$ = magnesium sulfate)

	Number of patients/exams	Signs of Vasospasm	p-level	Secondary infarction	p-level
DIND	$MgSO_4$ 32 pats Control 29 pats	$MgSO_4$ 9/32 Control 23/29	**p = 0.03**	$MgSO_4$ 0/9 Control 9/23	p = 0.167
DSA	$MgSO_4$ 40 exams Control 49 exams	$MgSO_4$ 26/40 Control 32/49	p = 1.00	$MgSO_4$ 2/26 Control 17/32	**p = 0.007**
TCD	$MgSO_4$ 234 exams Control 246 exams	$MgSO_4$ 114/234 Control 135/246	p = 0.48	$MgSO_4$ 7/114 Control 32/135	**p = 0.001**
PCT	$MgSO_4$ 210 exams Control 196 exams	$MgSO_4$ 117/210 Control 122/196	p = 0.51	$MgSO_4$ 10/117 Control 30/122	**p = 0.006**

the protective efficacy in experimental studies of permanent focal ischemia and consistently found reduced infarct volumes [1, 2, 20]. Likewise, a reduction of infarct volumes and improved neurological outcome was reported in animal models of temporary ischemia after intravenous administration of magnesium [3, 21]. However, after promising results of small clinical trials [5, 6], a large multicenter trial failed to show improved outcome after embolic stroke (IMAGES - Intravenous Magnesium Efficacy in Stroke Trial [22]). The authors concluded from their data that one of the most important reasons for the failure of the IMAGES-trial may have been the mean delay of 7 hours from onset of symptoms to beginning of treatment as neuroprotective efficacy decreases the longer administration is delayed [23].

In SAH, in turn, the prerequisites for a neuroprotective treatment are different. Delayed vasospasm of subarachnoid vessels appears in a high percentage of SAH patients within the first 2 weeks after SAH. Subarachnoid vessels become increasingly spastic and cerebral blood flow (CBF) may fall below ischemic thresholds [24]. This much-feared complication affects 20 – 30 % of SAH patients and may result in cerebral infarction, permanent morbidity or death. Delayed cerebral vasospasm after SAH is self-limiting after several days or weeks and, therefore, resembles a form of transient focal ischemia. On the other hand, this course of events bears the opportunity to undertake neuroprotective measures prior to the onset of ischemia. In an animal model of temporary middle cerebral artery occlusion (MCAO), a dose-finding study has demonstrated that the intra- and postischemic maintainance of serum concentrations between 2.0 and 2.5 mmol/l offered the highest neuroprotection [4]. Consequently, this dose was used in our clinical trial. We previously reported the absence of relevant side effects during the continuous long-term administration of magnesium sulfate in this dose and the prevention of secondary infarction [14]. Recently, the topic of magnesium has been re-caught and in an intraoperative setting during aneurysm surgery, the CBF-increasing properties been demonstrated [25]. In addition, further experimental [26] and clinical data [27-29] has been published suggesting a dose-dependent neuroprotective effect of parenteral magnesium.

In the face of these new activities in the topic, this post-hoc analysis was conducted specifically focussing on the neuroprotective property under conditions of critical brain perfusion after aneurysmal SAH. Our analysis shows that the incidence of pathological findings in TCD and PCT – parameters of arterial narrowing – are not overwhelmingly different between the two trial-groups indicating that the effect of magnesium in this concentration as a vasodilator may be secondary. Our finding that only 9 of 32 patients who were neurologically assessable in the magnesium group developed DIND while 23 of 29 in the control group developed DIND suggests that the ischemic tolerance may be increased by magnesium treatment. The findings that magnesium treatment decreases the incidence of infarction, once DIND has occurred, points into the same direction. Elevated flow velocities in TCD measurements and pathological findings in PCT are surrogate parameters which indicate arterial narrowing and reduced brain perfusion, respectively. The incidence of secondary infarction following these conditions was significantly reduced as well. Our results strongly suggest a neuroprotective effect of magnesium treatment after SAH.

The question arises why two large clinical trials have failed to show a beneficial effect in SAH-patients [15, 16]. Wong et al. reported about 327 patients that were randomized to receive a daily dose of 80 mmol/l $MgSO_4$ or

Table 2: Randomized clinical studies investigating the therapeutic effect of intravenous magnesium to prevent delayed vasospasm and secondary ischemic events and to improve outcome after aneurysmal subarachnoid hemorrhage. The results are not unequivocal. The beneficial effect might depend on the dose-regimen and comedication.

Author	Study setup	Treatment arms and comedication	Individuals	Results
Luo et al., 1996 [9]	Randomized, patient-blinded	$MgSO_4$ (approx. 100 – 200 mmol per day for 2 – 3 weeks) vs. placebo	52 patients	Significant reduction of secondary neurological deterioration, reduction of delayed cerebral infarction
Veyna et al., 2002 [8]	Randomized, patient-blinded	Nimodipine vs. nimodipine + $MgSO_4$ (25 mmol + 192 mmol/day for 10 days)	36 patients	Safe use of magnesium. Non-significant trend to improved clinical outcome
Van den Bergh et al., 2005 [37]	Randomized, double-blinded	Nimodipine vs. nimodipine + $MgSO_4$ (64 mmol/day for 14 days)	283 patients	Reduction of delayed cerebral ischemia and trend to better neurological outcome
Schmid-Elsaesser et al., 2007 [12]	Randomized, double-blinded	Nimodipine vs. $MgSO_4$ (10mg/kg + 30mg/kg/day for 7 days)	104 patients	No significant difference between magnesium and nimodipine
Muroi et al., 2008 [10]	Randomized, patient-blinded	Nimodipine vs. nimodipine + $MgSO_4$ (16 mmol + 64 mmol/24h, maximum serum concentration 2.0 mmil/l)	58 patients	Trend to better clinical outcome after 3 and 12 months. Treatment was stopped in 16 patients due to hypotension, arrhythmias, respiratory arrest and myocardial infarction
Wong et al., 2010 [15]	Randomized, double blinded	Nimodipine vs. nimodipine + $MgSO_4$ (20 mmol + 80 mmol/day for 14 days)	327 patients	No reduction of secondary ischemia or outcome
Westermaier et al., 2010 [14]	Randomized, double-blinded	$MgSO_4$ (141 ± 51 mmol – target serum level 2.0 – 2.5 mmol/l) vs. placebo	107 patients	Significant reduction of secondary infarction and ultrasonographic/angiographic vasospasm. Non-significant reduction of neurological outcome and mortality
Mees et al., 2012 [16]	Randomized, double-blinded	Nimodipine vs. nimodipine + $MgSO_4$ (64 mmol/day)	1207 patients	No improvement of clinical outcome

placebo. The authors reported no significant benefit of magnesium-treatment regarding clinical outcome after 6 months or clinical vasospasm [15]. The results of the largest clinical trial have been published by Mees and coworkers. In this multicenter study, 1,204 patients with aneurysmal SAH were enrolled and assigned to one of two study arms to either receive 64 mmol $MgSO_4$ per day or serve as controls. The administration of $MgSO_4$ did not improve clinical outcome assessed 3 months after SAH [16].

This data requires a critical analysis. In both trials, all patients – treatment and control group – were co-treated with nimodipine. This pyrrolopyrimidine-type calcium antagonist, has been intensively tested in various clinical studies in the 1980s and 1990s. Analyzing the pooled data for nimodipine trials, a Cochrane review revealed an advantage of nimodipine treatment, so that this treatment is routinely used in many centers. The review concludes, however, that the evidence for nimodipine was not beyond any doubt since the benefit of treatment is largely determined by one trial [30, 31]. The magnesium doses used in both trials were markedly lower than in our study in which 140 ± 51 mmol/d were administered to maintain the target serum parameters. In fact, dose regimens were used in those trials that had previously failed to prove a neuroprotective effect in stroke patients [32] and were neither tested in experimental settings nor in earlier clinical trials before launching the randomized trial. It is well known that magnesium has clear dose dependent effects [33]. New experimental data emphasizes that a neuroprotective action may not be exerted below a certain concentration [26]. Therefore, plasma concentrations need to be high enough. Our study used higher doses than other trials (Table 2) and – although it is a monocenter study – is the only one to investigate a dosing schedule that was a) controlled by serum levels, and b) tested for its neuroprotective efficacy in a preclinical experimental setting.

Our serum-level targeted dose-regimen was chosen on the basis of previous experimental studies that offered the highest neuroprotective effect in a model of temporary cerebral ischemia. On the other side, the co-treatment with nimodipine and magnesium is a simultaneous treatment with two calcium antagonists offering similar modes of action. Again, experimental studies have to be looked at and suggest that the neuroprotective effect of nimodipine may not be enhanced by combination therapies [34]. Schmid-Elsaesser et al. compared nimodipine treatment to magnesium treatment and found no marked and significant difference in the incidence of vasospasm and clinical outcome [12].

In the present study, 107 patients were randomized to either receive a placebo infusion or to receive a variable dose of intravenous $MgSO_4$ in order to maintain serum concentrations of 2.0 – 2.5 mmol/l for 10 days or – if there was clinical, angiographic and/or ultrasonographic vasospasm – until the signs of vasospasm had disappeared or to receive a placebo infusion without other calcium antagonists [14].

The fact that it resembles an incident-related rather than a patient-related analysis is a limitation of this study. A patient-related analysis has been reported previously [14]. It was, therefore, our purpose to investigate the tissue-protective effect of the compound once a sign of critical brain perfusion has appeared. The incidence-related assessment takes into account that a patient may have more than one episode of critical brain perfusion in the course of the disease and may react in a different way each time. However, it disregards that there may be a different degree of ischemic tolerance in each patient which may influence the risk of infarction and neurological recovery and make the analysis less precise. The choice of parameters that possibly indicate critical brain perfusion is another limitation of this analysis. Apart from clinical deterioration (DIND), all other parameters of this study indicating threatened brain perfusion (TCD, PCT, DSA) are surrogate parameters. We did not use absolute measures of CBF like thermodilution or Xenon-CT or single photon emission tomography in the daily routine, nor was it part of the study protocol. Although it is known today, that vasospasm is not the sole determinant of delayed ischemic deficits and infarction, it is widely accepted that reduced brain perfusion is a clear risk factor [35, 36]. All parameters used in this analysis are validated to indicate arterial narrowing or altered flow and tissue supply and perfusion at risk. Therefore, the results of this analysis suggest that, under these circumstances and if administered in an appropriate dose, magnesium can be neuroprotective in conditions of critical brain perfusion.

Conflict of Interest

None of the authors has a conflict of interest to declare.

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