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Vascular

Magnesium sulfate in the management of patients with aneurysmal subarachnoid hemorrhage: a randomized, placebo-controlled, dose-adapted trial

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Abstract

Background: Recent studies suggest that high-dose $MgSO_4$ therapy is safe and reduces the incidence of DIND and subsequent poor outcome after SAH. We intended to assess the safety and efficacy of high-dose $MgSO_4$ therapy after SAH as means to prevent DIND and to evaluate the impact on clinical outcome.

Methods: This was a prospective, randomized, single-blind, placebo-controlled study. The $MgSO_4$ infusion was adjusted every 12 hours until day 12 according to the target serum Mg^{2+} level. The occurrence of DIND, secondary infarction, side effects, and the outcome after 3 and 12 months were assessed.

Results: Fifty-eight patients were randomized; 27 received placebo and 31 $MgSO_4$. The difference in occurrence of DIND and secondary infarction was not significant. The intention-to-treat analysis revealed a trend toward better outcome ($P = .083$) after 3 months. On-treatment analysis showed a significantly better outcome after 3 months ($P = .017$) and a trend toward better outcome after 1 year ($P = .083$). Significantly more often hypotension ($P = .040$) and hypocalcemia ($P = .005$) occurred as side effects in the treatment group. In 16 patients (52%), the $MgSO_4$ therapy had to be stopped before day 12 because of side effects. No predictive factor leading to termination was found in a postrandomization analysis.

Conclusions: High-dose $MgSO_4$ therapy might be efficient as a prophylactic adjacent therapy after SAH to reduce the risk for poor outcome. Nevertheless, because of the high frequency of the side effects, patients should be observed in an intensive or intermediate care setting.

Keywords: Subarachnoid hemorrhage; Vasospasm; Magnesium sulfate; Randomized placebo-controlled dose-adapted trial

1. Introduction

With early aneurysm clipping, DIND due to cerebral vasospasm has become the most common cause of death and disability after aneurysmal SAH [6]. Recent studies suggest that high-dose $MgSO_4$ therapy is safe and reduces the incidence of delayed cerebral ischemia and subsequent poor outcome after SAH (Table 1) [4,5,13,14,17-21,23,24]. However, optimal dosages are under discussion and results are not yet definitive. The objectives of the present monocenter, prospective, randomized, single-blind,

Abbreviations: Ca2+, calcium; CT, computed tomography; DIND, delayed ischemic neurologic deficit; ECG, electrocardiogram; GOS, Glasgow Outcome Scale; MCA, middle cerebral artery; Mg^{2+}, magnesium; $MgSO_4$, magnesium sulfate; SAH, subarachnoid hemorrhage; TCD, transcranial Doppler sonography; V_{mean}, mean blood flow velocity; WFNS, World Federation of Neurological Surgeons.

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Table 1
Comparison of previously published pilot studies with continuous $MgSO_4$ applications in patients with SAH

Study	Design	n	$MgSO_4$ appl.	Dose and target level	Monitoring	End points	Positive results	Comedication	Side effects
Boet and Mee [4]	Monocenter, uncontrolled	10	Start within 5 d, for 10 d	Bolus: 20 mmol/20 min, cont.: 80 mmol/d dose-adapted, target $[Mg^{2+}]$: 2× baseline or 2.0-2.5 mmol/L	BP, ECG, $[Mg^{2+}]$	CVS: TCD and clinical, GOS after 3 mo	CVS: TCD (n = 5), GOS 4-5: n = 8	Nimodipine	No serious side effects, transient flushed feeling
Veyna et al [21]	Monocenter, randomized, placebo-controlled, single-blind	40	Start within 3 d, for 10 d	Bolus: 25 mmol/30 min, cont.: 144 mmol/d dose-adapted, target $[Mg^{2+}]$: 1.6-2.3 mmol/L	BP, ECG, $[Mg^{2+}]$, $[Ca^{2+}]$	CVS: TCD and clinical, GOS after 3 mo	Trend in patients with H&H II for better GOS	Nimodipine, phenytoin, Ca-gluconate if $[Ca^{2+}]$ <0.9 mmol/L	No serious side effects, $[Ca^{2+}]$ lower in treatment group, supplemented
Chia et al [5]	Monocenter, historical control group	23	Start within 5 d, until discharge from ICU	Bolus: none, cont.: 24-52 mmol/d dose-adapted, target $[Mg^{2+}]$: 1.0-1.5 mmol/L	BP, ECG, $[Mg^{2+}]$	CVS: angio, outcome scale (1-4) after 3 mo	Significantly less angio CVS	Nimodipine	No serious side effects
Van den Bergh et al [17]	Monocenter, uncontrolled, dose finding study	14	Start within 2 d, for 14 d	Group A—bolus: 16 mmol, cont.: 16 mmol/d, group B—bolus: none, cont.: 30 mmol/d, group C—bolus: none, cont.: 64 mmol/d	BP, ECG, $[Mg^{2+}]$ every other day	DCI, rebleeding, GOS	Optimal dosage: 64 mmol/24h, no DCI and all GOS 4-5 in group C	Nimodipine	No serious side effects, transient flushed feeling in group A
Van Norden et al [20]	Monocenter, randomized, placebo-controlled, double-blind	94	Start within 4 d, for 14-18 d	Bolus: none, cont.: 64 mmol/d	BP, ECG, $[Mg^{2+}]$ every other day	Side effects and termination	See side effects	Nimodipine	Termination due to hypermagnesiemia (n = 3), hypotension (n = 1), renal failure (n = 1)
Van den Bergh et al [18]	Multicenter, randomized, placebo-controlled, double-blind	283	Start within 4 d, for 14-18 d	Bolus: none, cont.: 64 mmol/d	BP, ECG, $[Mg^{2+}]$ not obligatory	DCI, new hypodensity in CT with DCI, mRS after 3 mo	Risk reduction for DCI: 34%, risk reduction for poor outcome: 23%	Nimodipine	Termination due to hypotension (n = 1), bradycardia and atrial fibrillation (n = 1), hypermagnesemia (n = 1)
Yahia et al [24]	Monocenter, uncontrolled	19	Start within 3 d, for 10 d	Bolus: none, cont.: 97 mmol/d dose-adapted, target $[Mg^{2+}]$: 1.5 -4.0 mmol/L	BP, ECG, $[Mg^{2+}]$, [glucose], [phenytoin]	CVS: TCD, angio, clinical, new hypodensity in CT, GOS after 1 mo	CVS: TCD n = 5, angio n = 9, clinical n = 2, CT: no ischemic infarction, GOS 4-5: n = 18	Nimodipine, phenytoine	No serious side effects
Wong et al [23]	Monocenter, randomized, placebo-controlled, double-blind	60	Start within 2 d, for up to 14 d	Bolus: 20 mmol/20 min, cont.: 80 mmol/d dose-adapted, target $[Mg^{2+}]$: 2× baseline, <2.5 mmol/L	BP, ECG, $[Mg^{2+}]$	CVS: TCD, clinical, GOS and BI after 6 mo	Trend to less TCD and clinical CVS, duration of TCD CVS significantly shorter	Nimodipine, valproate	No serious side effects
Prevedello et al [13]	Monocenter, controlled: standard therapy + $MgSO_4$ vs standard therapy only	72	Start at time of admission until discharge from ICU	Bolus: 20 mmol/20 min, cont.: 100 mmol/d dose-adapted, target $[Mg^{2+}]$: 2× baseline, <2.6 mmol/L	BP, ECG, $[Mg^{2+}]$	CVS: TCD, clinical	Patients with CVS required less hospitalization time if they received mg^{2+}	Nimodipine	No serious side effects
Schmid-Elsaesser et al [14]	Monocenter, randomized, controlled: $MgSO_4$ vs nimodipine	130	Start within 4 d, for 7 d PO, then 7 d IV	Bolus: 0.4 mmol/kg body weight in 30 min, cont.: 1.2 mmol/kg body weight per day	BP, ECG, $[Mg^{2+}]$	CVS: TCD, angio, clinical, new hypodensity in CT, GOS after 1 y	No difference	–	No serious side effects
Stippler et al [16]	Monocenter, historical control group	76	Start after verification of SAH, for 12 d	Bolus: none, cont.: 100 mmol/d	ICU setting (not described in detail) $[Mg^{2+}]$	CVS: clinical and new hypodensity in CT or angio, TCD and CT perfusion, GOS, mRS, BI, and SF-36 after 3 mo	Significantly less CVS, trend to better outcome based on mRS	Nimodipine	No serious side effects

Appl. indicates application; cont., continuous infusion; $[Mg^{2+}]$, serum Mg^{2+} level; $[Ca^{2+}]$, serum Ca^{2+} level; BP, blood pressure; CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; angio, angiographic; H&H, Hunt and Hess; mRS, modified Rankin scale, BI, Barthel index; SF-36, 36-item short-form health survey subscale; ICU, intensive care unit, IV, intravenous; PO, per oral.