revisão

Serum Magnesium Levels and Neurological Outcome After Acute Ischemic Stroke

O Nível Sérico de Magnésio e o Prognóstico Neurológico Após Acidente Vascular Cerebral Isquêmico Agudo

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ABSTRACT

Introduction. Stroke is the second most common cause of death worldwide. Approximately a third of survivors are functionally dependent at one year and it is the commonest cause of neurological disability in the developed world. Protecting the brain from ischemic damage remains a major target for stroke researchers. Many clinical trials tried to prove the efficacy of magnesium administration in stroke patients, but none have investigated the relationships between serum magnesium levels and outcome. **Method.** We prospectively analyzed 83 stroke patients enrolled in a cohort study between 2009 and 2010 and studied 30 and 90-day outcome data. In stroke survivors univariate Cox regression models and Kaplan–Meier plots were used to determine subject characteristics associated with an increased hazard of recurrence. Serum magnesium levels were measured daily during the hospital stay. Independent status was defined as Glasgow Outcome Scale grades 4 or 5 and Rankin Modified Scale 0 to 2. **Results.** Magnesium < 1,8 mg/dl were founded in 20 out of 83 patients (24%). There was no effect of low magnesium levels on rates of functional independence (28% versus 29%, *P*=0.84) or mortality (46% versus 45%, *P*=0.93). **Conclusion.** Serum magnesium levels were not associated with worse outcomes in our series.

Keywords. Serum Magnesium Levels, Stroke, Outcome.

RESUMO

Introdução. O Acidente Vascular Cerebral Isquêmico á a segunda causa mais comum de morte no mundo. Cerca de um terço dos sobreviventes são funcionalmente dependentes em 1 ano. Agentes de proteção cerebral permanecem o principal desafio de pesquisas. Muitos ensaios clínicos tentaram provar a eficácia da administração de magnésio nestes pacientes, mas nenhum investigou a relação entre níveis séricos de magnésio e o prognóstico. **Método.** Analisamos prospectivamente 83 pacientes através de estudo tipo coorte entre 2009 e 2010 e prognóstico em 30 e 90 dias foi avaliado. Modelo de regressão de Cox e Kaplan Meier foram usados para determinar características subjetivas associadas ao risco de recorrência. Níveis séricos de Magnésio foram dosados diariamente durante a permanência hospitalar. A independência funcional foi definida como níveis nas Escala Prognóstica de Glasgow 4 ou 5 e Escala de Rhankin modificada 0 a 2. **Resultados.** Magnésio < 1,8 mg/dl foi encontrado em 20 dos 83 pacientes (24%). Não houve efeito de baixos níveis séricos de magnésio nas taxas de independência funcional (28% versus 29%, *P*=0.84) ou mortalidade (46% versus 45%, *P*=0.93). **Conclusão.** Os níveis séricos de Magnésio não foram associados com pior prognóstico em nossa série de pacientes.

Unitermos. Níveis Séricos de Magnésio, AVE, Prognóstico Neurológico.

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INTRODUCTION

Stroke is the second most common cause of death worldwide[1]. Each year, about 795,000 people suffer a stroke in the United States[1] and about one million strokes in the European Union[2], making it by far the most common neurological disorder[3]. The mortality rates in Brazil are the highest in Latin America and became the first cause of death[4]. Approximately a third of survivors are functionally dependent at one year and it is the commonest cause of neurological disability in the developed world[2,3]. Stroke also causes secondary medical problems, including dementia, depression, epilepsy, falls and fractures. In the UK, the costs of stroke are estimated to be nearly twice those of coronary heart disease[5,6], accounting for about 6% of total National Health Service (NHS) and Social Services expenditure[6].

Protecting the brain from ischemic damage remains a major target for stroke researchers[7-16]. Lots of neuroprotective agents have been studied so far; however, none of them has been shown to be clearly efficacious for patients with stroke[7-19]. Magnesium, an important cofactor in metabolism and protein synthesis, joins into a complex with adenosine triphosphate acting as a noncompetitive NMDA receptor blocker; it inhibits the release of excitatory neurotransmitters at the presynaptic level and blocks voltage-gated calcium channels[20-22]. Moreover, it has been shown to suppress anoxic depolarization and cortical spreading depression -- both potential targets for neuroprotective treatment[7,9,11,12,14,17,21]. Many clinical trials tried to prove the efficacy of magnesium administration in stroke patients, but none investigated the relationship between serum magnesium levels and outcomes[13,15,17,18,19,23,24].

This study investigated whether or not lower magnesium serum levels were associated with worse outcome in patients with acute ischemic stroke.

METHOD
Patients

Between January 2009 and December 2010, 83 adult patients were selected to a prospective cohort study at Hospital Ipiranga – SUS – São Paulo. The inclusion criteria were as follows: 1) sudden onset of neurological deficit confirmed by a neurologist and presence of ischemic area on CT compatible with deficit; 2) patient age > 18 years old; 3) patient admission within the first 24 hours postictus; 4) any clinical grade accepted provided a reasonable prospect of survival. Exclusion criteria included concomitant or recent acute myocardial infarction, recent (≤ 30 days) surgery prior to the event, and/or previous stroke. In addition, patients who died before completing 10 days of treatment were not included. Patient demographics, clinical status on admission (GCS scores), head CT scans, admission and daily neurological examinations were recorded. It was approved by the local ethics committed (021/11).

Procedure

Serum magnesium levels were measured daily during the hospital stay. Our practice designates a low magnesium level that requires treatment to be <2.0 mg/dl. However, our laboratory standard measurement carries a ±0.2 mg/dl error; therefore, to ensure that patients designated to be in the low magnesium group had low serum magnesium concentrations, we defined our low magnesium group as a serum magnesium level <1.8 mg/dl at any point during this period.

Statistical Analisis

Logistic regression models were constructed to determine whether magnesium level was associated with independent status or mortality. Age and Glasgow coma scale (GCS) score were categorized according to cutpoints established in univariate analysis, as follows: (1) age: <69, 70 to 79, >80, (2) GCS: 3 to 10, 11 to 14, 15.

In stroke survivors, univariate Cox regression models and Kaplan–Meier plots were used to determine subject characteristics associated with an increased hazard of recurrence. The patients' clinical outcome was evaluated using the Glasgow Outcome Scale (GOS) and modified Rankin Scale (mRS) at discharge from our institutions, 30-days and 90-days outcome. Independent status was defined as GOS 4 or 5 and Rankin modified scale 0, 1 or 2. Statistical analyses were performed using SAS version 9.1.3.

RESULTS

Low Magnesium levels were founded in 20/83 (24%) patients. There was no effect of Mg < 1,8 mg/dl on

the rates of functional independence (28% versus 29%, P=0.84) or mortality (46% versus 45%, P=0.93). The multivariable-adjusted odds ratio for independent status in this group was 1.16 (95% CI 0.65 to 2.10, P=0.62).

Magnesium levels < 1,8 mg/dl was not associated with independent status or mortality (Table 1). We considered whether the magnesium levels might vary according to outcome definition or patient subgroups. There was no difference in 30-day or 90-day survival in Mg < 1,8 mg/dl.

DISCUSSION

The response to a lack of oxygen and nutrients (i.e., ischemia) by the brain includes a local release of chemicals that can damage brain cells, even beyond the damage that can be expected by ischemia alone[7,9,12,21,24]. Perhaps the most harmful of these chemicals is glutamate, an aminoacid used in very low amounts by brain cells to communicate with each other. During a stroke, however, the massive amount of glutamate released produces a flood of calcium inside brain cells which in turn causes them to die prematurely. Magnesium is thought to have the ability to prevent glutamate from causing this flood calcium in the cells, thus protecting them from premature death[8,9,11,13,14,16,25,26].

Currently, less than 10% of stroke patients can benefit from tissue plasminogen activator (TPA) infusions partly because of the time limit after the onset of stroke symptoms in which it can be used, and partly because it is contraindicated in hemorrhagic strokes[22].

Magnesium plays multiple roles in the normal function of our bodies: it exerts vascular effects, such as boosting vasodilatation, increasing the cardiac output, and prolonging bleeding time. Magnesium is used in eclampsia to prevent seizures, and also is a very well known antiarrhythmic agent[8,9,11-14,16,19,22,27,28].

Magnesium homeostasis in the central nervous system is regulated by active transport, and its concentration in cerebrospinal fluid (CSF) is maintained at levels higher than serum levels. With intravenous administration, magnesium concentration in CSF can be increased with a peak at 4 hours[10,15,29,30].

We did not detect any difference in outcomes in patients with lower or higher magnesium serum levels than 1,8 md/dl. By contrast, the effectiveness of magnesium in acute stroke has been demonstrated in animal studies. Early studies using rats and mice showed that if given at high concentrations, magnesium can decrease the area of the brain that is permanently lost as a result of a stroke. A meta-analysis of 4 trials in which magnesium was administered to patients with acute stroke yielded an 8% absolute reduction in risk of death or dependence after 3-6 months from disease onset[7]. However, the combined cohort of patients included in this systematic review was small (less than 200 patients). The results of a small, randomized trial not included in this meta-analysis were more promising, with a trend toward a better functional outcome at 30 days in patients treated within 24 hours from onset vs controls[8]. The results of a large randomized trial, in which magnesium was administered intravenously less than 12 hours (median, 7 hours) from symptom onset, were disappointing. Magnesium not only failed to show any beneficial effect on death and disability at 90 days, but it slightly increased mortality

Table 1

Baseline Characteristics According to Magnesium levels

Characteristic	Mg < 1,8 mg/dl n= 20 (24%)	Mg > 1,8 mg/dl n=63 (76%)	p
Age	72,4 +/- 9,4	71,9 +/- 12,7	0,65
GCS	14 (6,15)	13 (6,15)	0,83
GOS 4 or 5 (90 day independence)	78%	79%	0,84
90 day mortality	16%	15%	0,93

Continuous variables displayed as mean SD, or median (25th percentile, 75th percentile).
GCS= Glasgow Coma scale; GOS= Glasgow Outcome Scale

(odds ratio [OR], 1.21; 95% confidence interval [CI], 0.98-1.5). However, the investigators found a beneficial effect in a subgroup of patients with lacunar strokes (OR, 0.7; 95% CI, 0.53-0.92) and also in patients with a mean arterial blood pressure that was higher than the median (OR, 0.78; 95% CI, 0.61-0.99)[9].

Intravenous magnesium sulfate administration during the hyperacute phase of stroke was shown to be safe in a small, open-label pilot trial, in which more than 70% of patients were treated less than 2 hours from symptoms onset. Dramatic early recovery was achieved in 42% of patients, and good functional outcome (modified Rankin scale ≤ 2) at 90 days post treatment was achieved by 69% of all patients and in 75% treated within 2 hours[10].

CONCLUSION

Serum magnesium levels were not associated with worse outcomes in our patient series. The current state of knowledge does not allow for the practical use of magnesium in human stroke. Some data are promising, and require further evaluation in randomized, large-scale studies.

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