

CHAPTER 8

Magnesium retention in Complex Regional Pain Syndrome type 1 patients

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Abstract

Following results of a pilot study evaluating the effects of intravenous magnesium in Complex Regional pain Syndrome type 1 (CRPS 1) patients, we hypothesized that a mechanism related to magnesium accessibility is involved in individual response to treatment. Therefore, magnesium retention in CRPS 1 patients was determined, and the relationship with observed pain reduction after intravenous magnesium treatment was assessed.

Twenty-five CRPS 1 patients meeting the IASP diagnostic criteria were evaluated. Patients' magnesium status was obtained with the magnesium retention test, whereby 0.56 mmol/kg magnesium was given intravenously. Patients with magnesium retention of more than 29% were considered magnesium deficient. Pain reduction was measured on an 11-point Box scale (7 days, 3 times daily) and the McGill pain questionnaire at baseline, and at 1 and 3 weeks after the intervention. Median percentage of retained magnesium was 26% IQR 14-35%, whereby twelve patients were considered magnesium deficient. Median box pain and McGill scores at baseline and follow-up did not differ significantly between deficient and non-deficient patients. However, for the magnesium deficient patients a significantly longer duration of pain reduction was observed and more subscales of the McGill questionnaire were improved compared to non-deficient patients.

The high percentage of patients considered magnesium deficient in our sample of CRPS 1 patients provide an indication for deficiency in magnesium accessibility in a subgroup of patients, possibly leading to prolonged sensitization of nociceptors and/or increased inflammatory response observed in CRPS 1. Indications with regard to a relationship between magnesium status and the occurrence of sensory symptoms, and differing response to treatment with magnesium should be evaluated further.

Introduction

Complex Regional Pain Syndrome type 1 (CRPS 1) is a poorly understood pain syndrome which usually occurs after a trauma and is characterized by autonomic and motor disturbances (1). Sensory complaints of CRPS 1, such as spontaneous pain, allodynia and hyperalgesia, have been related to changes on NMDA receptor level resulting in central sensitization (2). The excessive release of glutamate by C and A δ -fibres and subsequent expulsion of the voltage dependent magnesium block, is induced by inflammatory mediator activity (Reactive Oxygen Species, neuropeptides, cytokines (3)) in response to trauma and (neurogenic) inflammation (3-6), resulting in activation of the NMDA receptor. This causes calcium influx into the cell which triggers a cascade of events that result in neuronal sensitization and abnormal pain sensations. Recently, we have performed a pilot study whereby intravenous administration of magnesium, a physiological NMDA receptor blocker, resulted in significant reduction of pain in acute CRPS 1 patients (7). However, individual response to magnesium intervention differed, resulting in clear responders and non responders. Therefore, we hypothesized that a mechanism related to magnesium availability could be related to differing individual response to treatment.

Magnesium is an essential intracellular cation which is involved in numerous biological processes. These processes include control of the protein and nucleic acid system, cell growth and energy metabolism (8). The importance of magnesium status has been illustrated in animal studies, whereby rats fed with magnesium deficient diets developed sensitization of nociceptive pathways and generalized inflammation (9;10). These pathophysiological process' could be reversed by administration of magnesium (10). Possibly, prolonged sensitization of nociceptors and/or increased inflammation in CRPS 1 can be induced or maintained as a consequence of reduced magnesium availability in a part of the patient population, providing a possible explanation of the observed variability. Substantial reduction of dietary intake of magnesium in western society over the last decades lends support to this assumption (11).

Magnesium levels can be measured in the intracellular (in muscle, bone, red blood cells) and extracellular compartment with the use of a variety of measurement techniques. Since little is known about the exchange of magnesium among body tissues and/ or extracellular fluids, abovementioned measurements provide only limited information about magnesium status (12). The magnesium retention test or magnesium load test is a more accurate test to determine total body magnesium status (12). With the magnesium retention test the percentage of retained magnesium of a fixed amount of administered magnesium IV can be

calculated. The percentage of retained magnesium is negatively correlated to the total magnesium status. In the present study, the magnesium status obtained by means of the magnesium retention test of patients with acute and chronic CRPS 1 was determined, starting from the assumption that differences between patients with low and normal total body magnesium status are present which relate to their reaction to intravenous magnesium administration.

Methods

Patients

Twenty-five acute and chronic CRPS 1 patients participating in a randomized placebo controlled trial (RCT) examining the effects of intravenous magnesium were recruited at the outpatient pain clinic of the VU University Medical Center. Patients had to meet the following inclusion criteria: 1. Diagnosis of CRPS 1 according to the IASP criteria (13); 2. A visual analogue Scale (VAS) for spontaneous pain of 5 cm or higher in the previous week; 3. Age between 18 and 70 years old; 4. CRPS 1 of one extremity. 5. Ability to provide written informed consent. Patients were excluded in case of: 1. Another chronic pain syndrome interfering with pain ratings; 2. Other complaints interfering with functional tests; 3. Known kidney and/or severe liver disease; 4. Creatinine levels exceeding the normal range (06-50 μ mol/l); 5. Active infection; 6. Malignant disease; 7. Heart failure; 7. Pacemakers or implanted defibrillators; 8. Pulmonary congestion; 9. Pregnancy. The study was approved by the Medical Ethical Committee of the VU University Medical Center.

Gastrointestinal and renal magnesium losses

Many diseases, conditions and drugs, such as diabetes mellitus, crohn's disease, hyperaldersonism, chronic alcoholism, diarrhea, loop and thiazide diuretics and proton-pump inhibitors are known to interfere with magnesium intake and secretion (8;14). Therefore, diseases associated with magnesium deficiency, the frequency (never, occasionally, frequently, always) of diarrhea using the Trend Symptoms Inventory (15) and the use of drugs that induce magnesium losses were assessed at baseline.

Magnesium retention test and sample collection

Patients were given 0.56 mmol/kg Mg (70 mg/kg MgSO₄) in 4 hours. Twenty-four hours urine samples were collected one day before the start of the magnesium infusion for determination of baseline magnesium and creatinine levels, and from

start of magnesium sulphate infusion for 24 hours for determining post infusion magnesium and creatinine levels. The percentage of retained magnesium was calculated using the formula according to Ryzen et al (12) (see figure 1). Baseline serum magnesium levels were obtained just before the start of the infusion.

Figure 1: Percentage of retained magnesium calculated according to Ryzen et al (12)

$$\% \text{ Mg retained} = 1 - \frac{\{ \text{postinfusion Mg} - \text{preinfusion Mg} \}}{\text{total elemental Mg infused}} \times 100$$

$$\text{where, preinfusion Mg} = \text{preinfusion Mg} \times \frac{\text{postinfusion creatinine}}{\text{preinfusion creatinine}}$$

Patients received magnesium infusions for 5 days as part of a RCT. Patients allocated to placebo during the trial period were offered the possibility to receive the magnesium infusion in above mentioned amounts after termination of the trial (open study). ECG monitoring was performed continuously during the administration of the study medication.

Magnesium retention and response to magnesium treatment

Secondary to measuring magnesium retention in CRPS 1, the influence of the magnesium status on the efficacy of 5 days magnesium administration in the reduction of pain was described. Spontaneous pain was recorded by patients on an 11-point Box scale 3 times daily for a period of one week. Pain type was assessed with the McGill pain questionnaire (16), expressed in the number of words chosen (NWC) and the pain rating index (PRI) for the whole questionnaire (total) and the sensory (s), affective (a) and evaluative (e) subscales. Assessments were performed before the start of the intervention (baseline), and at 1 (T1) and 3 (T3) weeks after the intervention. In open trials, patients tend to be biased towards a beneficial effect of the intervention. Therefore, baseline, T1 and T3 pain outcomes pain (box pain score and McGill questionnaire) of the patients attending the RCT and open study were compared with each other.

Statistical analysis

The data were collected and analyzed using SPSS version 15. Magnesium deficiency was defined as a magnesium retention of more than 29% as suggested by Gullestad

et al. (17), because it approaches our study best as regards doses of administered magnesium. Patient characteristics of the patients with high and low magnesium retention were evaluated by using Student t test, Mann-Whitney U test and Fisher exact test.

Mann-Whitney U test was used to compare changes in pain levels as measured with the Box scale and McGill pain questionnaire (baseline vs. T1 and baseline vs. T3) between magnesium deficient and non magnesium deficient patients and between the RCT and open trial patients. Differences in baseline, T1 and T3 pain levels within magnesium deficient and within non magnesium deficient patients were evaluated using Wilcoxon signed rank test. Data were presented in mean (SD) and median (inter quartile range) when appropriate. A p value less than 0.05 was considered statistically significant.

Results

The magnesium retention test was determined in 25 patients of which 12 received the magnesium treatment in the randomized controlled phase of this study (table 1). Patients included in this study were mostly women (23 women vs. 2 men) and the majority of the patients had CRPS 1 in the lower limb (18 vs. 7 for the lower and upper limb, respectively). Patients had a mean age of 47.41 (SD10.92) and a median duration CRPS 1 complaints of 18 months (IQR 9.50-23.50). Patients did not suffer from diseases associated with magnesium deficiency and chronic alcoholism. Six patients used drugs that are known to induce renal magnesium excretion and 11 patients reported to have diarrhea at baseline.

Serum levels were normal and ranged from 0.70 to 0.98mmol/l. Median percentage of retained magnesium was 26% IQR 14%-35% for the whole sample, of which twelve patients retained more than 29% of the administered magnesium and were considered magnesium deficient. One patient (patient 25), excreted more magnesium than was administered, therefore a negative percentage of retained magnesium was found. No statistically significant difference between the patients with high and low magnesium retention were found for age (mean, 43.89y vs. 50.70y, $p = 0.11$), duration of CRPS 1 complaints (median, 15 months vs. 19 months $p = 0.65$), frequency of diarrhea (50% vs. 38%, $p = 0.70$) and the frequency of used drugs that induce magnesium loss (25% vs. 23%, $p = 1.00$).

Table 1: Patient characteristics and percentage of retained magnesium

Patient	Sex	age	Affected Extremity	CRPS duration (months)	Trauma	Serum Mg (Mmo/l)	Mg retention (%)	Mg def	Use of drugs that induce magnesium excretion	Frequency of diarrhea at baseline
1	Female	29	Right leg	22	Sport injury	0.92	15%	No	-	Never
2	Female	47	Left leg	5	Sprain	0.90	10%	No	-	Occasionally
3	Female	28	Right leg	3	Bruise	0.81	26%	No	-	Occasionally
4	Female	57	Left leg	24	Distortion knee	0.88	6%	No	-	Never
5	Man	42	Right arm	7	Human bite	0.83	35%	Yes	-	Never
6	Female	46	Left leg	23	Acute hernia	0.81	50%	Yes	Yes ^a	Occasionally
7	Female	50	Right leg	12	Fracture	0.81	35%	Yes	-	Never
8	Female	63	Left leg	30	Fracture	0.79	12%	No	-	Never
9	Female	53	Left hand	12	Fracture	0.82	33%	Yes	Yes ^a	Occasionally
10	Man	38	Left Leg	115	Joint trauma	0.71	34%	Yes	-	Occasionally
11	Female	34	Left leg	142	Tendon rupture	0.97	67%	Yes	-	Occasionally
12	Female	67	Left hand	19	Wrist trauma	0.98	18%	No	-	Never
13	Man	58	Right leg	120	Sprain	0.77	36%	Yes	-	Never
14	Female	52	Left leg	18	Fracture	0.70	11%	No	-	Never
15	Female	59	Left leg	19	Spontaneous	0.91	19%	No	Yes ^β	Never
16	Female	33	Left leg	14	Fracture	0.91	62%	Yes	-	Frequently
17	Female	47	Left leg	16	Spontaneous	0.91	35%	Yes	-	Never
18	Female	57	Left arm	9	Fracture	0.86	23%	No	-	Occasionally
19	Female	52	Left leg	20	Strain of tendon	0.81	26%	No	-	Occasionally
20	Female	48	Left leg	6	Fracture	0.94	32%	Yes	Yes ^β	Never
21	Female	61	Right arm	22	Operation	0.88	13%	No	Yes ^{α,β,γ}	Never
22	Female	47	Right leg	10	Crush injury	0.79	16%	No	Yes ^α	Frequently
23	Female	41	Left leg	30	Knee operation	0.80	77%	Yes	-	Occasionally
24	Female	31	Left arm	8	Contusion	0.84	58%	Yes	-	Never
25	Female	38	Right arm	13	Operation	0.89	-12%	No	-	Never

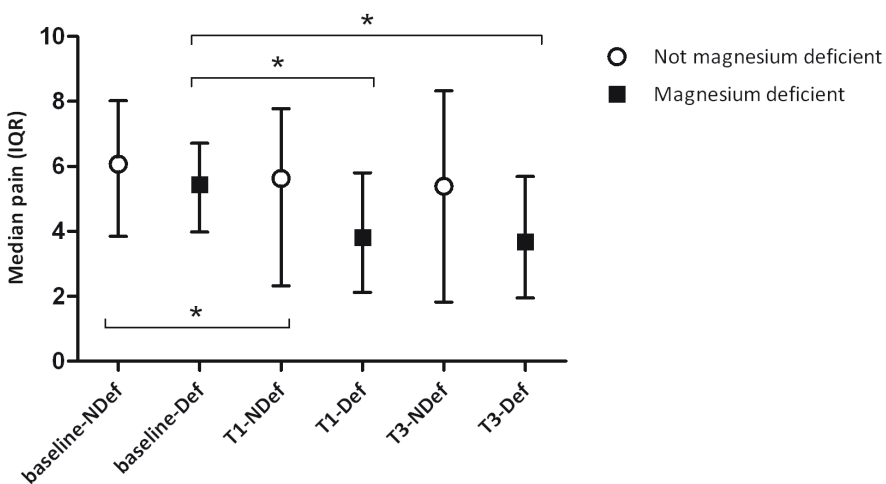
Patient 1-12: MRT measured during RCT. Patient 13-20: MRT measured during open trial. Mg def: magnesium deficient. ^α: Proton-pump inhibitor. ^β: Thiazide diuretic. ^γ: Loop diuretic.

Reduction in pain after 5 days of magnesium treatment measured with the Box scale and McGill questionnaire could only be established for 20 patients. Data of 5 patients (all open trial patients) were not included in the analysis. One patient received only 1 day magnesium infusion (patient 22), in 2 patients the 5 days magnesium treatment was not finished due to side effects (dizziness, headache, fainting, palpitation, patient 21 and 23) and in 2 patients pain recordings were missing (patient 24 and 25).

Pain

Figure 2 shows the median pain scores at baseline and Δ pain reduction at T1 and T3 for the magnesium deficient and the non magnesium deficient patients. Median box pain scores at baseline, and changes in pain at T1 and T3 did not differ significantly between magnesium deficient and non magnesium deficient patients (baseline: 5.45 IQR 3.97-6.71 vs. 6.07 IQR 3.84-8.02, $p = 0.74$, Δ pain reduction at T1: 1.71 IQR 0.35-2.20 vs. 0.63 IQR 0.22-1.69, $p = 0.22$, Δ pain reduction at T3: 1.09 IQR 0.43-3.65 vs. 0.21 IQR -0.14-2.21, $p = 0.17$). Evaluation of changes in pain within the group of magnesium deficient patients, showed statistically significant reduction of pain at T1 ($p = 0.007$) and at T3 ($p = 0.007$) compared to baseline. In the group of patients that were not magnesium deficient, pain was significantly reduced at T1 ($p = 0.03$), but not at T3 ($p = 0.14$) compared to baseline. Median pain at baseline, T1 and T3

Figure 2: Median box pain scores at baseline, T1 and T3 for the magnesium deficient and non magnesium deficient patients



* $p < 0.05$, wilcoxon, follow-up compared to baseline. IQR = inter quartile range.

did not differ significantly between the patients in which the magnesium retention test was measured during the RCT or during the open study (baseline box pain : 5.79 IQR 4.07-8.01 vs. 5.42 IQR 3.50-7.63, $p = 0.73$, Δ pain reduction at T1: 0.62 IQR 0.30-1.96 vs. 1.30 IQR 0.53-1.88, $p = 0.73$, Δ pain reduction at T3: 0.43 IQR -0.04-2.64 vs. 0.92 IQR -0.03-2.84, $p = 0.68$).

McGill

Data for the McGill pain questionnaire are shown in table 2. Comparison of changes between baseline, T1 and T3 McGill pain questionnaire scores showed no significant differences between magnesium deficient and non magnesium deficient patients (range: $p = 0.08$ to 1.00). Within the magnesium deficient patients, a significant improvement was found for the McGill NWct, PRIt, NWCs, PRIs, NWCe, PRle, NWCa and PRLa at T1 and for PRLa at T3 compared to baseline (range: $p = 0.005$ to 0.05). For patients that were not magnesium deficient, only PRIt, PRLa at T1 and NWCa at both T1 and T3 (range: $p = 0.04$ to 0.05) were significantly improved compared to baseline. Furthermore, no statistically significant difference were found for the McGill questionnaire scores between the patients in which the magnesium retention test was measured during the RCT or during the open study (McGill questionnaire: range $p = 0.12$ to 1.00).

Table 2: Baseline McGill pain questionnaire values and median changes at T1, T3 for patients with high and low magnesium retention

	magnesium deficient			Not magnesium deficient		
	Baseline	Change at T1	Change at T3	Baseline	Change at T1	Change at T3
NWCt	11.50(9.00-16.50)	4.50(2.50-8.50)*	0.00(-1.50-7.50)	10.00(8.00-14.50)	1.00(-2.00-3.75)	0.00(-2.00-4.75)
PRIt	20.00(14.75-24.00)	9.00(5.25-13.50)*	0.00(-1.50-13.00)	21.00(14.00-22.50)	4.00(1.75-9.25)*	3.50(-1.25-10.25)
NWCs	6.00(6.50-8.75)	3.00(0.00-5.25)*	0.00(-2.50-6.50)	11.00(7.00-13.00)	0.00(-1.00-3.00)	-0.50(-1.25-4.00)
PRIs	11.00(9.75-14.00)	5.50(1.50-9.00)*	1.00(-1.50-9.50)	13.00(7.50-16.50)	4.50(-1.00-7.25)	1.00(-2.00-6.55)
NWCe	3.00(2.00-3.00)	1.00(0.00-1.00)*	1.00(0.00-1.00)	2.00(1.50-3.00)	0.00(-0.20-0.25)	0.00(-0.25-0.25)
PRLe	5.00(4.00-6.25)	1.50(0.00-2.75)*	1.00(-0.50-2.50)	4.00(3.00-6.50)	0.00(-1.00-2.50)	0.00(-1.50-2.00)
NWCa	2.50(1.00-4.25)	1.00(0.75-2.50)*	1.00(0.75-2.50)	2.00(2.00-3.50)	0.50(-1.00-2.00)*	0.50(-1.00-2.00)*
PRLa	2.50(1.00-5.00)	1.50(0.00-2.75)*	1.00(0.00-2.00)*	4.00(2.50-5.00)	0.00(-1.00-2.50)*	0.50(-0.25-2.50)

NWC = number of words chosen, PRI = pain rating index, t = total, s = sensory subscale, e = evaluative subscale, a = affective subscale. *p < 0.05, wilcoxon, follow-up compared to baseline. Data in median (IQR).

Discussion

In the present study, the magnesium status obtained by means of the magnesium retention test of patients with acute and chronic CRPS 1 was determined, starting from the assumption that differences between patients in magnesium retention are present which relate to their reaction to intravenous magnesium administration.

We found a large variation in the percentage of retained magnesium in the present sample of CRPS 1 patients, in which half of the patients were considered magnesium deficient. The median percentage of retained magnesium (26% IQR 14-35%) found in our study was higher compared to studies of Ryzen et al. (12) and Gullestad et al. (17), who found in samples of healthy subjects after infusion with respectively 0.1 mmol/kg Mg and 28.92 mmol Mg mean magnesium retention of 15% (SEM 5) and 6.3% (SD 10.3). These dissimilarities in magnesium retention imply that our sample is deviating and indicates that our sample of patients as a group is imbalanced in magnesium body stores. In addition, higher doses of infused magnesium were used in our study compared to Ryzen et al.'s (12) and Gullestad et al.'s (17) studies. In case of our study, the dose of 0.56 mmol/kg may have exceeded the renal reabsorption capacity, resulting in an increase of renal magnesium excretion (12). Consequently, the presented number of patients with low magnesium availability could be an underestimation of the actual problem of magnesium deficiency in our sample.

Besides involvement of magnesium in disease mechanisms related to spinal NMDA receptors and central sensitization, NMDA receptors are also located in the periphery (18). Therefore blocking of peripheral NMDA receptors by magnesium may also contribute to reduction of peripheral sensory signs and symptoms of CRPS 1. Furthermore, magnesium deficiency has been shown to increase IL-6, TNF- α , substance P and oxidative stress (19-21), which are inflammatory mediators associated with CRPS 1 (3;22). Magnesium deficiency promotes vascular (23) and muscle (24) contraction and may therefore be involved in vasomotor disturbances and movement disorders observed in CRPS 1 (1). The association found between CRPS 1 and disorders with a known relationship with magnesium level imbalance (25-28) such as asthma, migraine, osteoporosis and menstrual cycle-related problems (29), provides further support to our hypothesis that subjects with lowered magnesium availability may be more susceptible to develop and maintain CRPS 1.

Several reasons can be provided for the body magnesium stores observed in our patients. In western society, magnesium intake in general has decreased either due to food processing, and/or our unhealthy diet (30). Magnesium is absorbed from dietary intake by the intestines. Patients with inflammatory bowel diseases

such as crohn's disease are known to exhibit magnesium deficiency, probably as a consequence of increased intestinal permeability (31) and malabsorption of magnesium (32). Also in CRPS 1 patients, intestinal permeability was found to be significantly increased compared to sex and age matched healthy controls (33). Furthermore, diarrhea, which has been associated with magnesium deficiency is a frequent complaint of CRPS 1 patients (15;34). We found no difference in the frequency of diarrhea between the magnesium deficient and the non magnesium deficient CRPS 1 patients. However, most of our patients reported to experience diarrhea occasionally, while particularly, chronic diarrhoea is known to cause magnesium loss.

Commonly used drugs such as loop and thiazide diuretics and proton-pump inhibitors are known to induce magnesium loss (8;14). Although in our sample of CRPS 1 patients, the use of these medications was not associated with higher percentage of magnesium retention, there are indications from a population based study for a possible association between antihypertensive drugs and CRPS onset. De Mos et al. found a statistically significant association between CRPS 1 and Angiotensin converting enzyme (ACE) inhibitors use. This association was stronger after long term ACE inhibitor use. Long term ACE inhibition, is associated with weak and insufficient aldosteron suppression (35) which known to cause magnesium loss by increasing urinary magnesium excretion (35). Possibly, the increased aldosteron levels, as a consequence of long term ACE inhibitions may be involved in lowering magnesium body levels in CRPS 1. In addition, a possible association between proton-pump inhibitors use and CRPS 1 should also be evaluated.

We found a significant decrease in median box pain scale at both T1 and T3 in the group of patients considered magnesium deficient, whereas for the non magnesium deficient patients pain was only significantly decreased at T1. Furthermore, more subscales of the McGill questionnaire were significantly improved in the magnesium deficient patients compared to the patients with normal magnesium status. These findings suggest a relationship for patients' response to the magnesium treatment with regard to their magnesium status. The positive reaction to magnesium administration in these patients suggest a more prominent role for the NMDA receptor. For non responding patients with magnesium deficiency, however, the administered amount of magnesium may well have been insufficient to block the NMDA receptors, because a proportion of the infused magnesium is used to supplement magnesium body stores. Dose-response studies for intravenous magnesium infusion in established magnesium deficient patients may provide more insight in this matter.

Additional considerations with regard to the present study have to be taken into account. This study reports about a limited number of CRPS 1 patients fulfilling specific inclusion criteria. Therefore, these results cannot be generalized to the general CRPS 1 population without restrictions. Furthermore, the CRPS 1 patients in general is heterogeneous with respect to clinical profile and possible prevailing underlying pathophysiological mechanism. Taken together, these findings suggest that problems associated with magnesium deficiency could be present in only a subgroup of CRPS 1 patients. A subgroup based approach for patient identification and treatment have been made in recent CRPS 1 literature (36-38).

Conclusion

The high percentage of retained magnesium in the present study provide indications for involvement of mechanism associated with impaired magnesium availability in a subgroup of CRPS 1 patients. The observed low magnesium status may be related to dietary intake, drug use or disease specific factors. Whether the prolonged sensitization of nociceptors and/or increased inflammatory response observed in CRPS 1 can be induced or maintained as a consequence of reduced magnesium availability, needs to be further evaluated.

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