CHAPTER 7

Intravenous Magnesium for Complex Regional Pain Syndrome type 1 (CRPS 1) patients: a pilot study

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Abstract

Objectives: To explore the feasibility of intravenous magnesium administration as a potential candidate intervention for a large size trial in CRPS 1. Design: Randomized clinical trial. Setting: Outpatient pain clinic. Patients: Ten CRPS 1 patients. Interventions: Eight patients received 70 mg/kg Magnesium sulphate infusions in 4 hours for 5 days. For blinding purposes, 2 patients received equal amount NaCl 0.9% solutions (data not analyzed or presented). Interventions were accompanied by standardized physical therapy.

Outcome measures: Pain was assessed using a 11-point Box scale (3 times daily for a week) and the McGill pain questionnaire. Skin sensitivity was measured with the Semmes Weinstein Monofilaments, (other) impairments with the Impairment Level Sumscore. In addition, functional limitations (RSQ, QRSD) and quality of life (SF-36, EuroQol) were evaluated. Assessments were performed at baseline, 1, 3, 6 and 12 weeks after intervention.

Results: Mild systemic side effects were experienced and the infusions were locally well tolerated. Pain was significantly reduced at all follow up compared to baseline (T1: p= 0.01, T3: p=0.04, T6: p=0.02, T12: p= 0.02). McGill sensory subscale improved significantly at T1 (NWCs: p=0.03 and PRIs: p=0.03). Impairment level (p= 0.03) and quality of life (EuroQol p= 0.04, SF-36 physical p= 0.01) were significantly improved at T12. No improvement was found for skin sensitivity and functional limitations.

Conclusion: Intravenous magnesium significantly improved pain, impairment and quality of life and was well tolerated. The results of this pilot study are encouraging and suggest that magnesium IV as a treatment in CRPS 1 should be further explored in a large size formal trial design.

Introduction

Complex Regional Pain Syndrome type 1 (CRPS 1) is a painful disorder of the extremities that may occur after trauma. CRPS 1 is characterized by autonomic and motor dysfunction in combination with sensory complaints, such as spontaneous pain, allodynia and hyperalgesia (1-3).

Release of Reactive Oxygen Species (ROS), neuropeptides and other mediators of inflammation (cytokines) (4) associated with an excessive (neurogenic) (5) inflammatory response (4;6;7), have been suggested to play a role in development or maintenance of CRPS (4;6;8;9). This cascade involving (peripheral) trauma and inflammation may consequently induce sensitization of local structures (C and Aδ-fibers), which elicit the release of glutamate. Continued release of glutamate activates AMPA receptors by calcium release (10). The calcium influx in turn depolarizes and releases the voltage dependent magnesium block and awakens the dormant NMDA receptors. Activation of the N-methyl D-aspartate (NMDA) receptors is key in the induction and continuation of peripheral and central sensitization (11-13), a process whereby structures involved in sensory processing are upregulated, resulting in an increased reaction to peripheral stimuli. This process of central sensitization and wind up (14) has been related to the occurrence of sensory complaints exhibited by CRPS 1 patients (15).

To counter this wind-up phenomenon and the vicious circle of sensitization, NMDA antagonists may be used (16). Evidence in acute as well as chronic pain treatment suggests that magnesium (17-19), a physiologically competitive calcium antagonist, down regulates the activation of the NMDA receptors responsible for the generation of neuropathic pain (20). Two recent placebo controlled RCT's, on magnesium IV in patients suffering from post herpetic neuralgia, and chronic pain patients of various etiology revealed a significant reduction of pain (20-22).

To our knowledge, the effects of magnesium on sensory disturbances in CRPS 1 patients has not been evaluated before. In the present pilot study, the feasibility with respect to efficacy, safety and tolerability of a magnesium IV treatment on pain and other sensory complaints, functional status and quality of life was evaluated in CRPS 1 patients.

Methods

Patients

CRPS 1 patients 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 (23); 2. A visual analogue Scale (VAS) for spontaneous pain of 5 cm or higher in the previous week; 3. age between 18 -70 years old; 4. CRPS 1 in one extremity. 5. Patients had to give written informed consent. Patients were excluded in case of: 1. Another (2nd) chronic pain syndrome, interfering with pain ratings; 2. Other complaints interfering with functional tests; 3. Known kidney and/or severe liver disease; 4. Active infection; 5. Malignant disease; 6. Heart failure; 7. Pacemakers or implanted defibrillators; 8. Pulmonary congestion; 9. Pregnancy.
Medication for the treatment of CRPS 1 (e.g. DMSO-crème and N-acetylcysteine), analgesics with NMDA antagonistic properties (ketamine, lidocaine, methadon, amandatine, dexomethorfan) and the use of (oral) magnesium, had to be stopped for the duration of the trial, starting one week before the onset of the trial. The study was approved by the Medical Ethical Committee of the VU University Medical center.

Intervention
In total, 10 patients were planned to be included in this study. Potential side effects of Magnesium IV are mandatory reported in the patient information brochure. To limit the effect of bias due to expectancy and placebo effect as observed in open trials, two patients were allocated to placebo. Eight patients assigned to the magnesium group received 70 mg/kg Magnesium sulphate continuously administered in 4 hours via an intravenous infusion (in two 50 ml syringe) of 24 ml/hour a day for a period of 5 days. The patients assigned to placebo received an equal amount of NaCl 0.9% solution (two 50 ml syringes) through a similar procedure. Treatment allocation was performed at random using a digital random number generator. Patients, researcher and the physician were blinded for the type of intervention for the duration of the trial. As the placebo intervention was added for blinding purposes only, the data of these patients were not presented or analyzed in this study. Success of blinding was assessed at the end of the trial, by asking patients and researchers what intervention they thought the patients had received.

Concomitant use of analgesics (with the exception of strong opioids) was allowed and was given according to the guidelines established by the World Health Organization (WHO) (24) and was registered daily in a pain diary. Regardless of the allocated intervention, all patients received standard physical therapy, given by a local therapist according to a fixed treatment protocol (8;25).

Measurements
Measurements were performed before the start of the intervention and at 1 (T1), 3 (T3), 6 (T6) and 12 (T12) weeks after the intervention. The assessments were carried out at the same time (e.g. morning or afternoon), under environmentally stable conditions, and were performed by a trained researcher according to a standardized protocol (with the exception of the questionnaires, which were filled out by the patients). The researcher attended regular training sessions 3 times per year in order to promote standardization of measurement.

1. Sensory measurements
Patients had to record their pain on an 11-point Box scale 3 times daily for a period of one week in a pain dairy before each measurement.
The McGill pain questionnaire (26) was recorded at each measurement point, and expressed in the number of words chosen (NWC) and the pain rating index (PRI) for the whole questionnaire (total) and the sensory, affective and evaluative subscales.

The sensitivity of the skin was objectively measured with Semmes Weinstein Monofilaments (SWM) (27). By comparing sensory scores of the affected extremity with the unaffected extremity, sensory thresholds differences can be determined. Monofilaments representing sensory cut off points as established by the manufacturer were used, each representing a different force (ranging from 0.0045 to 447.0 grams), whereby the procedure started with the smallest filament up to the largest. The testing area's for the (palmar side of the) hand were the distal phalanx of dig.1, the distal and proximal phalanx of dig.2, the distal and proximal phalanx of dig.5 and hypothenar of dig. 5 were tested. The feet were tested on the plantar side: the distal phalanx dig.1, the distal phalanx dig.2, the distal phalanx dig.5, the arcus plantaris medialis and the arcus plantaris lateralis.

2. Impairment level assessments
Patients impairment level was assessed with the Impairment Level Sumscore (ISS) (28;29), in which pain (during movement) as measured by Box scale and the McGill pain questionnaire; temperature measured with infrared thermometer (First Temp Genius®) (30); volume measured with water weight volume measurements; and active range of motion (AROM) measurements were converted into a compound sumscore. The ISS ranged from 5 to 50 whereby higher scores corresponded to higher levels of complaints.

3. Activity level assessments
The Radboud Skills Questionnaire (RSQ) (31) and the Walking questionnaire (WQ) and questionnaire rising and sitting down (QRSD) (32) were used to address the activity level of CRPS 1 patients for the upper and lower extremity respectively.

4. Quality of life assessments
The Short Form-36 (SF-36) (33) and EuroQol (34) were used for the assessment of quality of life. The SF-36 was assessed at baseline and T12. In addition to the SF-36, the EuroQol was also assessed at T3.

5. Safety and tolerability measurements.
Prior to the start of the intervention, creatinine levels and cardiac function (using 12 leads ECG) were determined in each patient. Plasma levels of magnesium were recorded each infusion day prior to and after the intervention, in the (unaffected) arm.
ECG monitoring was performed continuously during the administration of the study medication up to 15 minutes after termination of the intervention.
Possible systemic and local side effects and adverse events were recorded during intervention by the researcher and registered by patient in the pain diary and evaluated according to European guidelines (35).

Statistical analysis:
The data were processed and analyzed using SPSS version 11. Median week pain scores were calculated for the Box scale per patient. Total and subscale pain scores for the McGill pain questionnaire were determined per patient. Mean SWM scores for the feet calculated per patient, were used to determine median sensory differences between the affected and unaffected foot. Sumscores were calculated for the ISS and its constituting items per patient. Furthermore, mean total scores were calculated for the RSQ, the WQ&QRSD, EuroQol and for the physical and mental domain of the SF-36 per patient.
Descriptive as well as comparative statistics were used, whereby the Wilcoxon test was used to compare follow up data with baseline values in the magnesium group. Baseline group scores and changes at follow up compared to baseline were defined in medians and inter quartile ranges.

Efficacy of magnesium

Definition of efficacy of magnesium was determined a priory. Magnesium was considered to be sufficiently effective for further evaluation if: 1. At least 4 out of 8 patients receiving magnesium had a reduction of spontaneous pain of 50% or more as measured with the Box scale. 2. Or an improvement of 2 or more of the outcomes sensitivity (measured with McGill pain questionnaire and SWM), impairment, activity or quality of life were found.

Results

From April 2005 to 2007, 14 CRPS 1 patients were included from the outpatient clinic of the VU University Medical Center, from a total of 59 patients fulfilling the inclusion criteria (see figure 1).

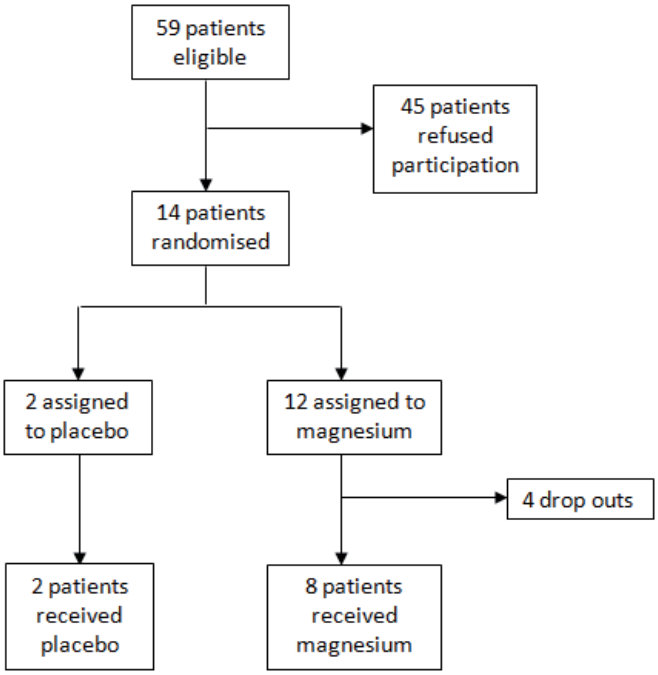


Figure 1: Flow of eligible subjects

Reasons for not participating in the pilot study for the remaining 45 patients fulfilling the inclusion criteria were; wishing conventional treatment with DMSO-crème and n-acetylcysteine (N=7); fear of injections and infusions (N=6); unwilling to receive placebo (N=7); fear of side effects of magnesium (N=2); intensity of intervention (N=9); work related reasons (N=7); unwilling to participate in research (N=2); other

Table 1: Patient characteristics, pain and complaints of central sensitization at baseline

	Patient characteristics						Aspects of central sensitization at baseline					
	Patient	**Man/ woman**	**Age (years)**	**Upper/lower extremity**	**Duration CRPS (days)**	**Initial trauma**	**Pain**	**Allodynia**	**Hyperesthesia**	**Hypoesthesia**	**Hyperalgesia**	**Hypoalgesia**
Mg	1	Man	59	Upper	61	Dupuytren or.	***Yes***	No	No	No	No	No
	2	Woman	31	Lower	83	Sprain	***Yes***	No	No	No	No	No
	3	Woman	53	Upper	151	Fracture	***Yes***	***Yes***	No	No	No	No
	4	Woman	48	Upper	103	Fracture	***Yes***	***Yes***	***Yes***	***Yes***	***Yes***	No
	5	Woman	18	Lower	102	Fracture	***Yes***	No	No	No	***Yes***	No
	6	Man	30	Upper	64	Spontaneous	***Yes***	No	***Yes***	No	***Yes***	No
	7	Woman	62	Upper	123	Fracture	***Yes***	No	No	No	***Yes***	No
	8	Woman	65	Upper	176	Fracture	***Yes***	***Yes***	***Yes***	No	***Yes***	***Yes***
Pla	9	Woman	21	Lower	82	Sprain	***Yes***	***Yes***	***Yes***	No	***Yes***	No
	10	Woman	53	Upper	112	Fracture	***Yes***	No	No	No	No	No

Mg= magnesium, Pla= placebo.

(N=5). No significant differences between participants and non participants were found for age and gender (Age: participants; 47.03 SD (15.95), non-participants; 46.37 SD (14.22), p=0.81; Percentage male/female: participants; 21.4%/78.6%, non-participants; 23.9%/76.1%, p= 0.87), and for relevant clinical characteristics (participants versus participants: median pain at first presentation at the outpatient clinic (7.00 IQR (5.75-8.00) vs. 6.00 IQR (5.00-7.50)) p=0.29; occurrence of allodynia: (50% vs. 30%) p=0.69; hyperesthesia (28% vs. 30%) p=0.72; hyperalgesia: (54% vs. 37%) p=0.16; hypoesthesia: (29% vs. 32%) p=0.64; hypoalgesia: (7% vs. 11%) p=0.53; edema: (100% vs. 83%) p=0.42; skin temperature differences: (86% vs. 94%) p=0.15).

Of 14 initially included patients, 3 patients did not finish the infusion week. One patient dropped out after 3 infusion days due to side effects (dizziness, headache and pain in infusion arm). Two patients dropped out after respectively 3 and 1 infusion days due to emotional reasons, not related to the intervention. One patient was excluded from the analysis due to a protocol violation.

In total, 10 patients (8 women and 2 men, mean age 44.00 SD (17.44)) completed the trial. Patient characteristics are shown in table 1. All patients reported to have pain at baseline and all, except patient 1 and 2, experienced (reported and/or observed) additional signs and symptoms of central sensitization (table 2). Prior to the intervention, patients used Paracetamol 500mg (N=2), Naproxen 220mg (N=1), Diclofenac 50mg (N=1), Brufen retard 800mg (N=1), or no pain medication (N=7).

Table 2: Baseline values of performed measures

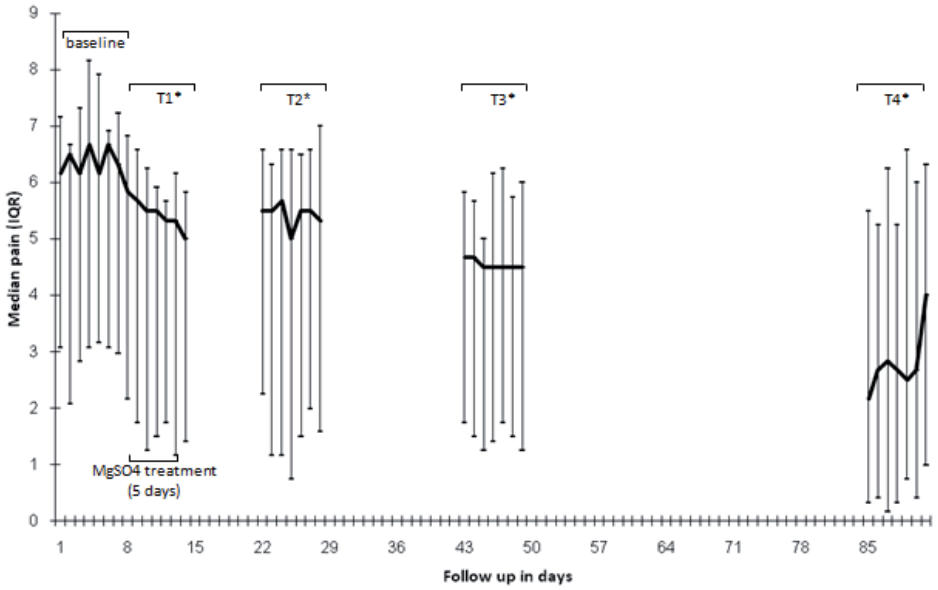
	baseline
Median week pain	6.67 (3.10-6.92)
Semmes Weinstein Monofilaments	0.15 (0.10-0.41)
ISS total	22.00 (17.25-25.75)
ISS box	7.50 (3.25-8.75)
ISS McGill	5.00 (3.00-5.00)
ISS temperature	1.50 (0.00-2.00)
ISS volume	3.00 (1.00-4.00)
ISS AROM	6.00 (4.25-7.75)
RSQ (N=6)	3.05 (1.80-3.30)
WQ & QRSD (N=2)	4.72 (4.63-4.80)
EuroQol	0.79 (0.53-0.80)
SF-36 Mental	74.00 (57.75-80.75)
Physical	50.50 (42.50-66.75)

ISS = Impairment Level Sumscore, RSQ= Radboud Skills Questionnaire, WQ&QRSD = Walking questionnaire and questionnaire rising and sitting down. Data in median (IQR).

1. Effects on sensory disturbances

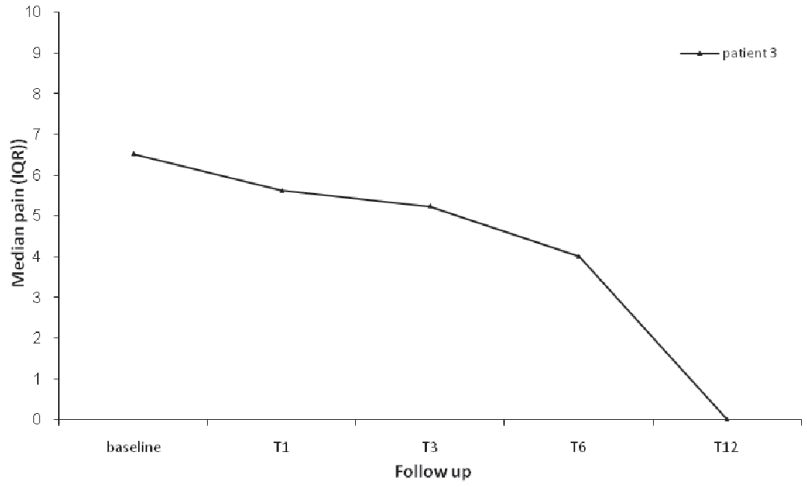
Figure 2 shows the median daily pain scores reported by patients. A significant reduction in pain week scores was found at all follow up measurements compared to baseline (baseline values are presented in table 2) for patients receiving magnesium (T1: p=0.01, T3: p=0.04, T6: 0.02 and T12: p=0.02 respectively). At T12 the median box pain was 2.66 (IQR 0.37-5.50) (median pain reduction of 2.19 (IQR: 1.62-2.52)). All patients showed a decrease of median week pain scores at T12 compared to baseline. A 50% decrease in pain intensity was observed at T12 in 4 patients (median pain decrease 72% (IQR: 54.8-90.3%)), the remaining 4 patients had a median pain decrease of 20.6% (IQR: 7.2-35.8%). The lowest and highest decrease in median box pain scores at T12 were, 0.58 (patient 6, pain decrease of 6.6%) and 6.52 points (patient 3; figure 3, pain decrease of 100%). During the treatment, patient 6 experienced an inguinal hernia between measurement T6 and T12, which may have influenced the pain score measured at 12 weeks.

Figure 2: Median pain scores per day at baseline, 1, 3, 6 and 12 weeks after magnesium treatment (N=8)



*p< 0.05, Wilcoxon, follow-up compared to baseline. Data in median (IQR).

Figure 3: Median pain scores per week for patient 3 at baseline, 1, 3, 6 and 12 weeks after magnesium treatment



Data for the McGill pain questionnaire are shown in table 3. A significant improvement was found for the McGill total number of words chosen (NWCt) at T1 compared to baseline (NWCt: median reduction: 2.00 (IQR 1.00-4.00), p=0.03. In addition, a significant decline in NWC sensory and the value assigned to the chosen words (pain rating index) was found at T1 compared to baseline (NWCs: median reduction: 2.00 (IQR 2.00-3.00), p=0.03 and PRIs : median reduction: 4.00 (IQR 3.00-6.00), p=0.03). Furthermore, PRI evaluative improved significantly at T6 and T12 (median reduction of 1.00 (IQR 0.00-1.75), p=0.04 and 1.50 (IQR 0.00-3.50), p=0.04, respectively). No significant changes were found for PRI total, NWC evaluative and the affective subscale of the McGill pain questionnaire.

A reduction in absolute sensory thresholds differences as measured with the SWM, was found at all follow up compared to baseline (baseline values are shown in table 2) (median absolute sensory threshold reduction at T1: 0.06 (IQR –0.01-0.14), T2: 0.11 (IQR 0.04-0.16), T3: 0.07 (IQR -0.10-0.34), T6: 0.04 (IQR -0.01-0.37), T12: 0.05 (IQR 0.00-0.18). However, these improvements were small and not statistical significant. None of the 10 patients reported allodynia during SWM testing.

Table 3 : Baseline McGill pain questionnaire values and median changes at T1, T3, T6 and T12

	baseline	change at T1	change at T3	change at T6	change at T12
NWCt	9.00 (6.00-9.75)	2.00 (1.00-4.00)*	1.00 (-2.00-4.75)	1.50 (-1.00-4.50)	3.00 (-1.00-6.00)
PRIt	12.50 (11.25-15.75)	4.00 (1.00-9.00)	2.00 (-2.50-9.00)	5.00 (-1.50-9.75)	7.50 (1.00-11.75)
NWCs	5.50 (3.25-6.00)	2.00 (2.00-3.00)*	2.00 (-1.00-3.00)	1.50 (-1.25-3.00)	2.50 (-0.50-4.75)
PRIs	8.00 (6.00-11.50)	4.00 (3.00-6.00)*	2.50 (-0.75-6.75)	4.00 (-2.50-7.00)	5.50 (0.00-9.75)
NWCe	2.50 (2.00-3.00)	0.00 (-1.00-1.00)	0.00 (-1.00-1.00)	0.00 (0.00-0.75)	0.00 (-1.00-1.00)
PRIe	4.00 (3.00-5.00)	0.00 (-1.00-1.00)	1.00 (-1.00-2.50)	1.00 (0.00-1.75)*	1.50 (0.00-3.50)*
NWCa	1.00 (0.25-1.00)	0.00 (0.00-0.00)	0.00 (-0.75-1.00)	0.00 (0.00-0.00)	0.00 (0.00-1.00)
PRIa	1.00 (0.25-1.75)	0.00(-1.00-1.00)	0.00 (-0.75-0.75)	0.00 (-0.75-0.75)	0.50 (0.00-1.00)

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).

2. Impairment level assessment

The ISS at baseline (baseline values are presented in table 2) and differences scores at follow up are presented in figure 4. ISS values were predominantly moderate. A significant decrease of 3 points (IQR 1.00-7.00) was found at T12 compared to baseline (p= 0.03). Although this reduction was not clinically relevant for the group as a whole, 3 patients (patient 1, 3 and 5), showed clinical relevant improvement of 6.00, 8.00 and 7.00 points, respectively at T12 compared to baseline. Furthermore, a significant improvement was found for the ISS Box (pain during movement) (figure 5) at T1: improvement 1.00 (IQR 0.00-2.0), (p= 0.04), T3: improvement 2.00 (IQR 0.25-2.00), (p= 0.03) and T6: improvement 1.50 (IQR 1.00-2.00), (p= 0.02), and for the ISS AROM (figure 6) at T6: improvement 1.25 (IQR 0.00-1.75), (p= 0.02) and T12: improvement 1.00 (IQR 1.00-1.00), (p= 0.01). No significant differences were found on other ISS parameters (temperature, volume and McGill).

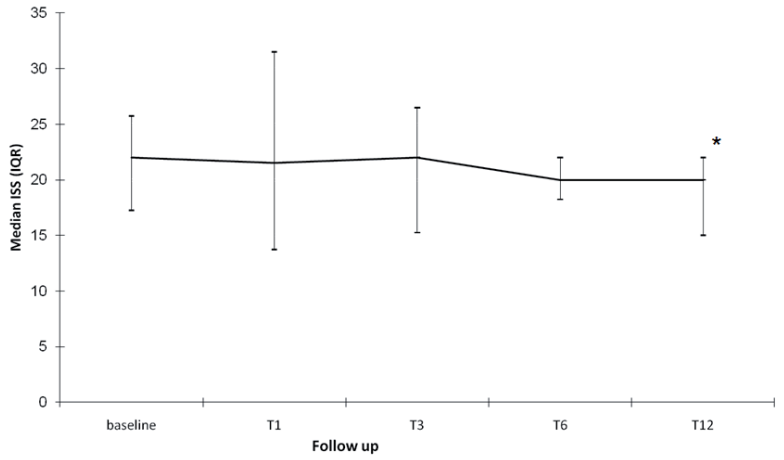
3. Activity level assessments

No significant change on activity level was found compared to baseline for the RSQ (T1: p= 0.95, T3: p= 0.35, T6: p= 0.11, T12: p= 0.05) and WQ&QRSD (T1: p= 0.71, T3: p= 0.68, T6: p= 0.50, T12: p= 0.71).

4. Quality of life

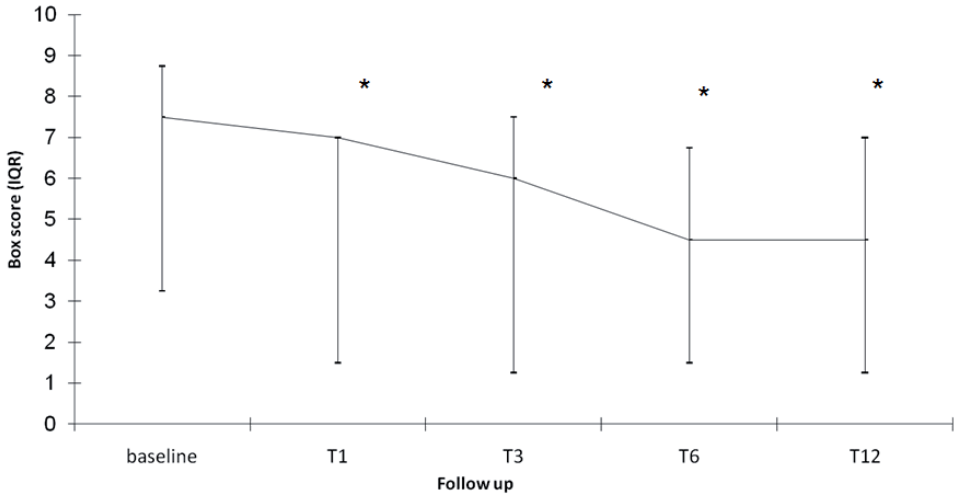
Scores of the EuroQol and of the physical health domain of the SF-36 improved significantly at 12 weeks compared to baseline (EuroQol improvement: 0.06 (IQR

Figure 4: ISS for patients at baseline, 1, 3, 6 and 12 weeks after magnesium treatment



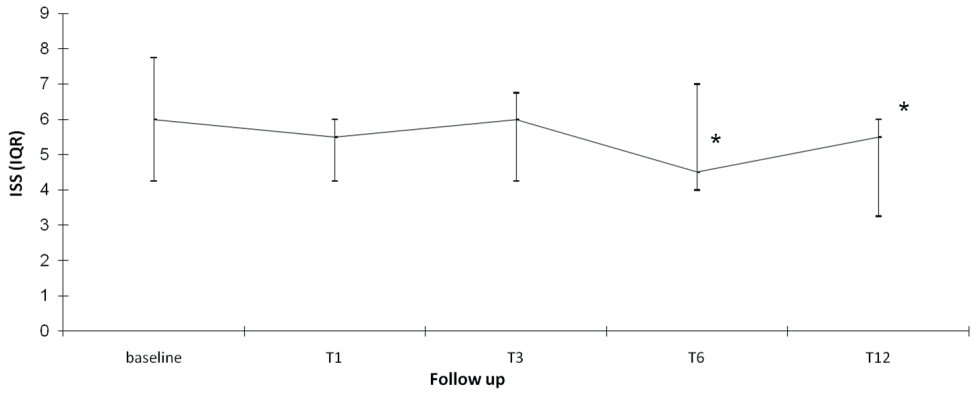
ISS= Impairment Level SumScore. *p< 0.05, Wilcoxon, follow-up compared to baseline. Data in median (IQR).

Figure 5: ISS Box pain during movement for patients at baseline, 1, 3, 6 and 12 weeks after magnesium treatment



*p< 0.05, Wilcoxon, follow-up compared to baseline. Data in median (IQR).

Figure 6: ISS AROM for patients at baseline, 1, 3, 6 and 12 weeks after magnesium treatment



*p< 0.05, Wilcoxon, follow-up compared to baseline. Data in median (IQR).

0.00-0.32)), p= 0.04 and SF-36 physical health improvement 9.50 (IQR 7.25-22.50), p= 0.01). Patient 3, 4 and 6 in particular showed improvement on the EuroQol (improvement 0.27, 0.34 and 0.47). An improvement on the physical domain of the SF-36 was seen in patients 3, 5 and 6 (improvement of 37.00, 21.00, 23.00 points respectively).

5. Tolerability and safety measurements

Patients receiving both interventions (placebo and magnesium) experienced mild side effects. Side effects for the magnesium group were; infusion site pain (N=5), flushing (N=4), nausea (N=2), vomiting (N=1), fatigue (N=4), headache (N=1), dry mouth (N=1), burning eyes (N=4), palpitations (N=I), dizziness(N=4), light-headedness (N=2) and diarrhoea (N=1). The 2 patients receiving placebo both experienced nausea and fatigue. All cannula were placed in the unaffected hand. In 5 patients the intravenous cannulation had to be replaced due to sensitivity at the infusion site. After replacement the cannula remained in situ uneventfully.

Four out of 8 patients receiving magnesium had elevated magnesium plasma levels at the first day after the start of the intervention (mean magnesium level of 1.25 (SD 0.23)), which normalized during the following days of the infusion. The remaining 4 patients exhibited normal magnesium plasma levels (between 0.70 and 1.00 mmol/l) during the course of the magnesium infusion. No serious adverse events were reported.

Success of blinding

Success of blinding was determined by asking patients and researcher which treatment they thought the patient had received. All patients thought to have received the magnesium treatment, including both patients receiving placebo. The researcher was not able to single out the 2 patients receiving the placebo infusion.

Discussion

The results of this pilot study show significant benefits of intravenous magnesium treatment on complaints and quality of life in CRPS 1 patients. Pain reported by patients was significantly decreased. Moreover, sensory disturbances as measured with the McGill NWCt, NWCs and pain rating index were significant improved at 1 week after magnesium treatment.

These results are in line with results of other studies with regard to the efficacy of magnesium on neuropathic pain, whereby pain scores were significantly lower after magnesium infusion administration compared to placebo in patients with postherpetic neuralgia (20) and after a single dose of intravenous magnesium, partial to complete pain relief was found in cancer patients with neuropathic pain up to 4 hours (22). In these studies, however, an immediate reduction in pain at 20 and 30 minutes was observed which may be related to the higher levels of magnesium administered in a shorter period of time than was the case in our study. We investigated the effect of magnesium administration for a substantially longer period, and found the pain rating to be significantly reduced up to 12 weeks.

These promising results may be indicative for the role of central sensitization in the development of (sensory) complaints. By blocking the NMDA receptor calcium channel, and preventing the influx of calcium and the initiation of an intracellular cascade, magnesium may impede peripheral and/or central sensitization resulting in a reduction of pain (36). Possibly, also other aspects of sensitization often displayed in CRPS 1, such as allodynia and hyperalgesia may be abolished after magnesium treatment. In the present study, only pain was evaluated at follow up, therefore no information can be presented at this point about the effect of magnesium on other aspects of peripheral or central sensitization.

An unexpected result of this study is the low baseline pain scores of some of our patients. Patients were recruited at our outpatient clinic during consulting-hours and were only included in our study if they had a VAS pain score of 5 or higher. After inclusion into our trial, 3 patients had lower baseline median pain scores. Patients

expectancies, disease progress and regression to the mean may have contributed to this drop in pain at baseline.

In addition to pain, patients also showed significant improvement on impairment as measured with the ISS. This improvement was, in contrast to the reduction of pain, only found at 12 weeks. Possibly, changes in indices measured with the ISS other than pain are modulated in a more gradual manner by the magnesium treatment. Furthermore, patients who participated in our study had relatively low baseline ISS scores compared to ISS scores of CRPS 1 patients in other studies (8;25). Possibly, the ISS was not able to decrease a lot due to already low ISS scores.

Besides the treatment with magnesium, all patients also received physical therapy according to a fixed treatment protocol (8;25). Although physical therapy was shown to have a positive effect on pain (37), we believe that the observed reduction in pain may be related to the administration of magnesium. In our study, the standardized physical therapy was started one week prior to baseline, and continued for the duration of the trial. Furthermore, the reduction of pain intensity was only observed after the start of the infusion week and not during the baseline week. However, we cannot exclude some beneficial effect of physical therapy at this point, and the applied physical therapy may have contributed to the improvement in impairment seen at 12 weeks.

This pilot study revealed only limited side effects following magnesium infusion. Four out of 8 patients receiving magnesium had normal plasma levels (between 0.70 and 1.0 mmol/l) the day following the infusion. The elevated magnesium plasma levels found in the other 4 patients receiving placebo might be explained by higher BMI indexes (mean BMI = 34.28 (SD 3.98) vs. 26.26 (SD 5.30)), resulting in higher doses of magnesium. Furthermore, intravenous magnesium is used in a broad range of indications (e.g. preeclampsia and eclampsia) and was shown to be safe and tolerable in studies using higher dosages than we have used in the present study (38;39).

One could argue, however, that the positive results found in this study could be attributed to the high probability of finding a significant differences using the current design with multiple testing (40). Although the probability of chance findings cannot be ruled out at this point, the high number of significant results found in this pilot study, which are in line with prior theoretical considerations with respect to the expected mode of action of magnesium in relation to the mechanism of sensitization presumed in CRPS 1 (15), would make this less likely in our opinion. Furthermore, the current research design makes it difficult to exclude the role of natural disease recovery and regression to the mean for these patients with a

relatively short disease duration. In a future study, the effects of magnesium should be evaluated for patients less prone to natural change in disease severity (i.e. patients with chronic CRPS 1). In addition, sensory disturbances associated with central sensitization may be even more prominent in chronic CRPS 1 patients (41) , making inclusion of this subgroup of patients even more relevant.
Consequently, we have started a Randomized Controlled Trial in which in a parallel design the effects of intravenous magnesium sulphate on pain, other aspects of central sensitization and impairment and in a group of acute and chronic CRPS 1 patients is investigated.

Conclusion

The significant improvement of pain, impairment and quality of life after the treatment with intravenous magnesium suggest that magnesium has beneficial effects on CRPS 1 complaints. Intravenous magnesium was well tolerated and resulted in mild side effects. These results are encouraging and suggest that the potential of IV magnesium as a treatment in CRPS 1 should be further explored in a large size formal trial design

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