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Original Research Article

Intravenous Magnesium for Chronic Complex Regional Pain Syndrome Type 1 (CRPS-1)

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Abstract

Objective. To assess the effects of intravenous administration of magnesium on complex regional pain syndrome type 1 (CRPS-1), a randomized double-blind placebo-controlled trial was performed.

Methods. Fifty-six patients with CRPS-1 (International Association for the Study of Pain Orlando criteria) received $MgSO_4$ 70 mg/kg or placebo (NaCl 0.9%) in 4 hours over 5 consecutive days. Pain (BOX-11 and McGill), the level of impairment (Impairment level Sum Score [ISS]), functional limitations (Radboud Skills Questionnaire, Walking Skills Questionnaire/questionnaire rising and sitting down), participation (Impact on Participation and Autonomy [IPA]), and quality of life (Short Form-36, EuroQol, IPA) were evaluated at baseline and at 1, 3, 6, and 12 weeks.

Results. No significant differences were found between $MgSO_4$ and placebo on the BOX-11 and ISS at different time points during the trial on intention-to-treat and per-protocol analysis. A significant improvement on the BOX-11 was found after the first week of the trial in both groups (mean 0.7; standard deviation 1.1). For the $MgSO_4$ group, a clinically relevant and statistically significant improvement on the ISS at 1 week (median 5, interquartile range [IQR] –1 to 8) and a significant improvement on the McGill up to 6 weeks (median 2 words, IQR 0–4.5) were found compared with baseline, which were not found in the placebo group. Significant improvement in perceived job participation was found for the $MgSO_4$ group at 12 weeks (median improvement 1.44–1.17; $P = 0.01$). ISS improved significantly more in patients with a low Hospital Anxiety and Depression Scale (HADS) score (≤10) in the $MgSO_4$ group (mean 4.4 vs mean –3.1; $P = 0.02$).

Conclusion. Administration of the physiological competitive N-methyl-D-aspartate receptor antagonist magnesium in chronic CRPS provides insufficient benefit over placebo. Future research should focus on patients with acute CRPS and early signs and symptoms of central sensitization.

Key Words. CRPS-1; NMDA Receptor; Magnesium; Central Sensitization

Introduction

Complex regional pain syndrome type 1 (CRPS-1) is a pain syndrome of an extremity, which mostly develops after trauma (e.g., distortion, fracture, or surgical intervention), and is characterized by disproportional pain, sensory disturbances, swelling, color changes, change in temperature, decreased motor function, and trophic changes [1]. Aberrant inflammation after trauma and subsequent peripheral and central sensitization are proposed as main mechanisms in the development and maintenance of CRPS-1 [2]. In the cascade of sensitization, excessive release of cytokines (e.g., tumor necrosis factor [TNF]α), substance P and calcitonin gene-related peptide, can lead to increased glutamate release in the central nervous system. Continued release of glutamate can activate the dormant N-methyl-D-aspartate (NMDA) receptor antagonist resulting in increased calcium influx into the synaptic cleft, therewith increasing the efficiency of synaptic transmission. The activation of the NMDA receptor is a crucial

step in the development of central sensitization, and is associated with spontaneous pain and increased reaction to peripheral stimuli [3]. Besides activation of NMDA receptors, local inflammation also are thought to lead to an increase in NMDA receptors density in peripheral tissue and sensory nerves, thereby further contributing to the process of sensitization [4,5].

To counter the process of peripheral and central sensitization and to reduce sensory disturbances, NMDA receptor antagonists have been proposed [6,7]. Studies by Collins et al. [8] and Sigtermans et al. [7,9] have shown significant decrease of pain in CRPS patients following intravenous administration of magnesium and ketamine. However, ketamine is associated with a broad spectrum of severe side effects [10], and costs of treatment are high. Magnesium is a physiological substance involved in many cellular processes, and is needed for catalyzation of enzymes and synthesis of DNA. In the nervous system magnesium acts as a competitive NMDA receptor antagonist, stabilizing abnormal nerve excitation. Because of its favorable physiological profile and relatively limited costs, magnesium has been used in treatment of various medical conditions with limited side effects [11]. Treatment with magnesium has been shown to significantly reduce pain in acute and chronic pain states [12,13]. Significant reduction of pain and sensory disturbances in acute stage CRPS patients were found on intravenously administered magnesium in a randomized, blinded pilot study [6]. However, the efficacy of this intervention in CRPS patients with long standing CRPS has not yet been investigated. Consequently, we performed a randomized placebo-controlled trial comparing magnesium sulphate IV ($MgSO_4$) with placebo IV (NaCl 0.9%), evaluating effects on pain, aspects of sensitization, level of impairment, activities, participation, and quality of life in CRPS-1 patients.

Methods

Patients

CRPS-1 patients diagnosed according to the International Association for the Study of Pain (IASP) Orlando criteria (IASP of 1994) were recruited at the outpatient clinic of the VU University Medical Center between June 2006 and December 2011. Inclusion criteria were a pain score higher than 5 on the BOX-11 scale before inclusion, age between 18 and 70 years, CRPS limited to one extremity, and patients had to give written informed consent. Exclusion criteria were other (pain)syndromes interfering with outcome or measurements, severe liver or kidney function disturbances, heart or lung diseases, active infection, pregnancy, mental retardation, psychiatric abnormality, or active malignant disease. Medication for the treatment of CRPS (e.g., dimethyl sulfoxide [DMSO] cream and N-actylcysteine), analgesics with NMDA antagonistic properties, and oral magnesium were stopped at least 1 week before starting the trial. Use of analgesics without antioxidative or NMDA antagonist properties were allowed during the trial. The Medical Ethical Committee of the VU University Medical Center approved the study (National Trial Registry [NTR] number: NTR1873).

Intervention

Patients were randomized to receive either magnesium sulphate ($MgSO_4$) 70 mg/kg or placebo (NaCl 0.9%) via intravenous infusion of 25 mL/h in 4 hours a day for a period of 5 consecutive days in indistinguishable syringes. These dosages were based on a previous pilot study resulting in positive results and limited side effects [6]. This dose is known to give minimal side effects, and is well below the dose given to preeclampsia patients [14,15]. There is extensive clinical experience with magnesium in a broad range of indications, such as preeclampsia/eclampsia [15], acute stroke [16], head trauma [17], postoperative pain [18], acute bronchospasm [19], and heart disease [20,21] (see NTR 1873 for further information).

The randomization was performed in blocks of four such that half of the patients receive $MgSO_4$ and the others placebo. The institutional pharmacist performed both blinding and randomization independently. The patient, researcher, and physician were blinded for the type of intervention for the duration of the trial. After the 12-week follow-up, when all measurements were performed, the code was broken to be able to offer the placebo patient group intravenous $MgSO_4$ in an off-label setting. Success of blinding was assessed at the end of the trial for each patient by asking the researcher and patient which intervention they thought the patient received. Concomitant use of analgesics was allowed and was given according to the Dutch multidisciplinary treatment guideline [22], and was registered in a medication diary. All patients received standard physical therapy according to a standardized treatment protocol [23]. As safety measurements prior to the intervention, creatinin levels and cardiac function (using an electrocardiogram [ECG]) were determined for each patient. Plasma levels of magnesium and calcium were recorded daily prior to and after the 4-hour intervention. ECG monitoring was performed continuously during administration of the study medication. Possible systemic and local side effects were recorded during intervention by the researcher and registered by the patient in the pain diary.

Assessments

Assessments were performed using a standardized assessment protocol used within the (Trauma RElated Neuronal Dysfunction) TREND consortium (http://www.trendconsortium.nl) using valid and reliable tools. The assessment protocol was based on the International Classification of Functioning, Disability and Health model [24], in line with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials guidelines [25] for evaluation of chronic pain. Primary effect measures were the Impairment level Sum Score (ISS) score evaluating the level of impairment in patients with CRPS, and the 11-point BOX scale, a numerical rating scale on severity of pain at 12 weeks after starting the trial.

Functioning

One week before the intravenous treatment (T0), during the administration of trial medication (T1), and 3 (T2), 6 (T3), and 12 (T4) weeks following the start of the intervention, patients filled out the 11-point BOX scale ranging from 0 (no pain) to 10 (most pain imaginable) for pain severity three times daily during 1 week [26]. The adjectives list of the Dutch version McGill Pain Questionnaire was filled out consecutive to the BOX-11 ratings in order to obtain the total number of words chosen (NWCt) and the pain rating index (PRI) [27,28].

The sensitivity of the skin (detection threshold) was measured with Semmes Weinstein Monofilaments (SWM) comparing the affected extremity to the contralateral extremity. Monofilaments representing different forces (0.0045–447.0 gr) were used starting with the smallest filament up to the largest. The testing areas for the hand were the palmar side of the distal phalanx of dig. 1, the distal and proximal phalanx of dig. 2, the distal and proximal phalanx of dig. 5, and the hypothenar of dig. 5. The feet were tested on the plantar side: distal on phalanx dig. 1, the distal phalanx of dig. 2, the distal phalanx of dig. 5, the medial and lateral arcus plantaris. The mean of the five tested areas was used to acquire an overall sensibility of the affected and contralateral extremity. The difference of skin sensitivity between the affected and nonaffected extremity was evaluated over time [29–31].

Impairment was assessed with the ISS, a validated score comprising the assessment of pain (Box-11, McGill score [NWCt]), and comparisons between the affected and contralateral extremity of temperature by means of an infrared thermometer, volume by means of water displacement volumeters, and active range of motion by means of standardized goniometers [32,33]. The ISS ranges from 5 to 50 whereby higher scores indicate higher levels of impairment. The measurements were carried out under environmentally stable conditions by a researcher that attended training sessions three times a year within the TREND consortium.

Activities

Functional limitations were assessed with the Radboud Skills Questionnaire (RSQ) (upper extremity) [34] or the Walking Skills Questionnaire (WSQ) and questionnaire rising and sitting down (QRSD) (lower extremity) [35]. Changes on the RSQ, WSQ, QRSD were analyzed at all time points.

Participation and Health

Participation was evaluated with the Impact on Participation and Autonomy (IPA) questionnaire, comprising the domains autonomy indoors (getting around and family role), and autonomy outdoors (getting around, social life/relationships, work/education) [36] at T0, T3, and T4. Quality of life was assessed with the Short Form-36 (SF-36) [37] and the EuroQol [38] at T0, T3, and T4.

Personal Factors

Subjective assessment of signs and symptoms and personal factors were evaluated using the TREND symptom inventory at T0, T3, and T4. Psychological assessments were performed at T0 using the Hospital Anxiety and Depression Scale (HADS) [39], the Tampa Scale for Kinesiophobia [40], and the Pain Coping Inventory (PCI) [41].

Sample Size Calculation

According to standard power calculation, 33 patients per group would have been required to detect a clinically relevant difference of two points on the primary outcome measurement BOX-11 ($\delta = 2$), with a significance level of $\alpha = 0.05$ and power $\beta = 0.1$.

Off-label Analysis

Patients assigned to the placebo group in double-blinded phase were offered the opportunity to receive intravenous $MgSO_4$ treatment after completing the 12-week follow-up period. Assessments during the off-label treatment consisted of pain diaries (BOX-11) and McGill questionnaires over 4 consecutive weeks. Evaluations were performed at 1 and 3 weeks after starting the intervention in order to parallel timing of assessments during the double-blinded phase. The last assessment of the double-blinded phase was used as baseline for the off-label trial.

Statistical Analysis

Data were stored in a NEN-7511 certified central web-based database (ProMISe®). Blind analyses were performed using SPSS version 15.0 (IBM, Armonk, NY, USA). Comparability of the treatment group and the placebo group on patient characteristics and prognostic measures was assessed at baseline, using Chi-square, independent sample *t*-tests or Mann–Whitney tests. Effects of treatment over time were analyzed using the paired student's *t*-test and Wilcoxon signed-ranks test. Differences between groups at the follow-up assessments were compared using the independent sample *t*-test or the Mann–Whitney *U*-test. Primary outcome (pain and ISS) was analyzed according to intention to treat as well as by per-protocol principles. Subgroup analyses were performed for gender, cold/warm extremity, and acute vs chronic CRPS (6 months or less) to evaluate effects of these characteristics on outcome using the independent sample student's *t*-test or the Mann–Whitney test. For all analyses, a two-sided *P* value lower than 5% was used to indicate statistical significance.

Results

Patient Characteristics

From June 2006 to December 2011, 56 patients were recruited out of 229 eligible patients with CRPS-1 according to the IASP Orlando criteria (Figure 1). The most

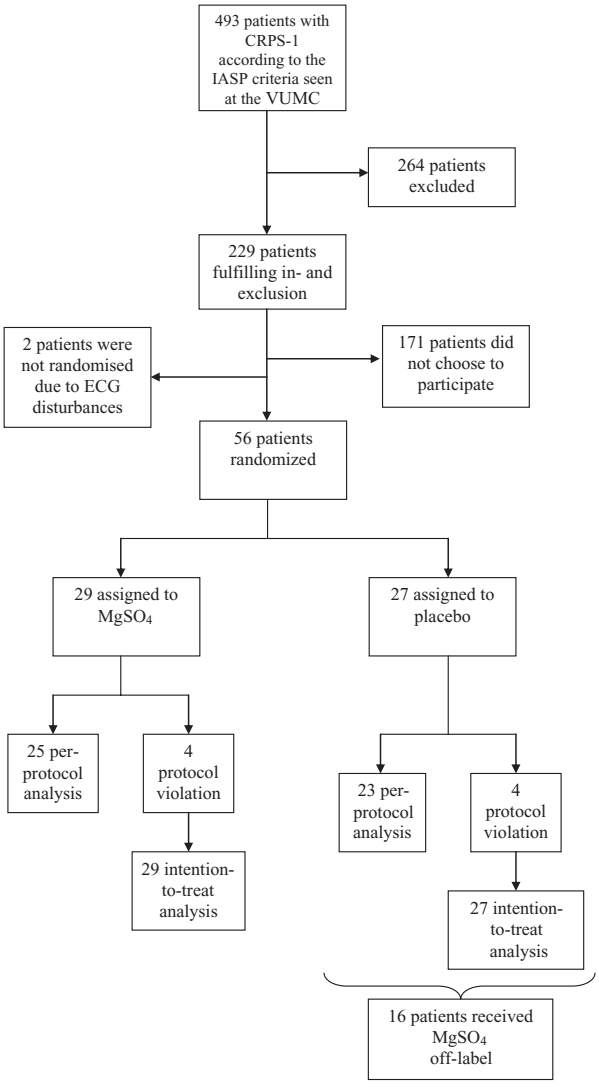

Figure 1 Flow diagram on selection, randomization and follow-up of studied patient groups.

prominent reasons for nonparticipation of eligible patients (N = 171) were that the study would be too time consuming/interfered with personal circumstances (36%), signs or symptoms resolved before entering the trial (18%), not wanting to postpone standard treatment (13%), fear of intravenous medication or needles (12%), or patients could not be traced (16%). Of the 56 included patients, 52 female and 4 male, 29 were assigned to receive $MgSO_4$ infusion and 27 received placebo infusion with NaCl 0.9%. Seven patients did not complete the intervention week (four assigned to $MgSO_4$, three to placebo), and one patient violated the protocol by starting DMSO in the period of the trial (assigned to placebo).

In the magnesium group, significantly more patients reported a colder affected extremity, and in the placebo group, more patients reported alternating temperature of the affected extremity; however, this did not lead to effect modification. The disease duration differed as well between both groups; however, this was not significant due to the large range and uneven distribution of this variable. Other differences in prognostic variables were not found between the patient groups (Table 1). Pain and ISS scores did not differ between patients with an upper or lower affected extremity at baseline or during the course of the trial (independent sample *t*-tests; *P* range 0.1–1.0). Differences between the upper or lower affected extremity in sensitivity to touch as measured with SWM were found as expected [31] (related to difference in tactile discrimination and thickness of skin between hand and foot); however, changes over the trial were similar for upper and lower extremity; therefore, results were pooled for all patients. Duration of CRPS at the start of the trial was not related to effects of the intervention on the BOX-11 and ISS; therefore, no subgroup analyses were performed concerning disease duration. Effects of treatment in patients with a high score on the HADS (>10) differed from effects on patients with low scores on the HADS (≤10); therefore, subgroup analyses for patients with low and high scores on the HADS are presented. Missing data ranged from 0.4% for the ISS to 11% for the McGill Pain Questionnaire.

Outcome

No significant differences were found between the $MgSO_4$-treated group and the placebo group on the primary effect measures BOX-11 and ISS at different time points during the trial on intention-to-treat and per-protocol analysis. Both groups showed a statistically significant improvement of 1 point compared with baseline on the BOX-11 scale on all time points up to 12 weeks after starting the trial (*P* 0.00–0.02) (Table 2, Figure 2). A clinically relevant and statistically relevant improvement of the ISS (5 points; $P < 0.05$) was found in the intervention group at T1 (Table 3, Figure 2), which was not found in the placebo group.

Pain as assessed with the McGill NWCt improved up to 6 weeks after baseline in the magnesium group; this differed significantly from the placebo group directly after the week of infusion ($P = 0.01$). This improvement could be attributed to the improvement in the sensory subscale of the McGill questionnaire (NWCs) ($P < 0.01$). The McGill PRI improved in both groups, but no differences were found between the magnesium and placebo group (Table 4, Figure 3). Sensitivity to touch as measured by SWM showed no significant change over time or significant differences between the groups (Table 5). Functioning measured by the RSQ and WSQ did not improve over time in either of the groups. Quality of life measured by the SF-36 did not change over the course of the trial, but the EuroQol improved significantly in the magnesium-treated group (median 0.43 at T0 to 0.56 at T3, $P = 0.05$) and not in the placebo group; however, no differences were found between groups. Participation and autonomy slightly improved in both groups (median 1.42–1.22; $P = 0.02$)

Table 1 Patient characteristics

	Total	Placebo	$MgSO_4$
N	56	27	29
Female/male	52/4	25/2	27/2
Age (years)*	46.7 (11.5)	46.1 (11.0)	47.2 (12.2)
Duration (months)†	16.0 (6.0–41.8)	10.5 (5.0–26.8)	23.0 (8.5–64.8)
Upper/lower extremity	16/40	10/17	6/23
Right/left	25/31	14/13	11/18
Initial trauma			
Fracture	15	7	8
Soft tissue injury	11	5	6
Operation	11	7	4
Nerve-related operation	3	2	1
Spontaneous	3	2	1
Wound	2	1	1
Other traumas	11	3	8
Initial temperature			
Warm	12	5	7
Cold	30	11	19
Alternating	13	10	3
Unknown	1	1	0
Mean NRS at baseline*	6.2 (1.7)	6.3 (1.6)	6.1 (1.8)
ISS score at baseline*	30.0 (6.6)	30.7 (6.9)	29.2 (6.2)
CRPS score at baseline*	12.2 (2.3)	12.8 (2.3)	11.6 (2.3)
RSQ at baseline† (N = 15)	2.9 (2.5–3.5)	3.0 (2.5–3.5)	2.8 (2.4–4.1)
WSQ at baseline†			
In-house	5.6 (2.0–7.1)	5.6 (2.3–7.8)	5.9 (1.7–7.1)
Outside	7.4 (4.7–8.3)	7.2 (4.2–8.1)	7.4 (5.1–8.6)
Sitting and rising	6.3 (3.3–8.9)	7.1 (4.6–9.1)	5.8 (2.6–9.1)
SF-36 at baseline*			
Vitality	49.2 (20.5)	50.4 (23.1)	48.0 (18.0)
Social functioning	63.6 (25.7)	66.4 (26.3)	61.0 (25.3)
EuroQol at baseline†	0.43 (0.20–0.78)	0.46 (0.18–0.78)	0.42 (0.20–0.75)
IPA at baseline†			
Autonomy inside	1.1 (0.7–2.0)	1.3 (0.6–2.0)	1.2 (0.7–2.0)
Autonomy outside	2.0 (1.6–2.8)	2.0 (1.6–2.8)	2.1 (1.7–3.0)
PCI at baseline*	69.3 (13.7)	67.0 (11.7)	71.3 (15.2)
TSK at baseline*	36.8 (7.3)	35.4 (6.5)	38.1 (7.8)
HADS at baseline†	8.0 (6–13.3)	8.0 (6.0–15.0)	8.0 (5.0–12.0)

* Mean (standard deviation [SD]).
† Median (interquartile range [IQR]).
CRPS = complex regional pain syndrome; HADS = Hospital Anxiety and Depression Scale; IPA = Impact on Participation and Autonomy; ISS = Impairment level Sum Score; NRS = numerical rating scale; PCI = Pain Coping Inventory; RSQ = Radboud Skills Questionnaire; SF-36 = Short Form-36; TSK = Tampa Scale for Kinesiophobia; WSQ = Walking Skills Questionnaire.

and for job participation only in the patient group treated with $MgSO_4$ improved (median 1.44–1.17; $P = 0.01$) (as measured with the IPA).

Subgroup Analysis

Patients with low HADS scores (≤10) improved significantly more on the ISS than patients with higher HADS scores (median 3.9 vs 0.7; $P = 0.05$). When analyzing this for both intervention groups separately, this change of ISS was statistically significant for the patients treated with magnesium (mean improvement of 4.4 vs deterioration of 3.1; $P = 0.02$) and not for the placebo group.

Off Label

Of the 27 patients who received the placebo in the double-blinded phase, 16 patients chose to receive $MgSO_4$ treatment after completion of the trial and were evaluated in the off-label phase (Table 6). Evaluation on the BOX-11 showed a significant mean improvement of

Table 2 Pain scores (NRS) at all time points (mean, standard deviation [SD])

	Baseline (T0)	T1	T2	T3	T4
All	N = 56	N = 55	N = 53	N = 54	N = 52
	6.2 (1.7)	5.3 (2.3)	5.4 (2.6)	5.3 (2.8)	5.2 (2.7)
Placebo	N = 27	N = 26	N = 26	N = 27	N = 25
	6.3 (1.6)	5.4 (2.3)	5.5 (2.4)	5.3 (2.5)	5.4 (2.3)
$MgSO_4$	N = 29	N = 29	N = 27	N = 27	N = 27
	6.1 (1.8)	5.2 (2.4)	5.3 (2.8)	5.2 (3.1)	5.1 (3.0)

NRS = numerical rating scale.

0.7 (standard deviation 1.0) after the treatment week ($P = 0.02$). Improvement on the McGill scale was found 1 week after starting the intervention (PRI total and sensory subscale) and after 3 weeks (NWC and PRI total).

Side Effects

Common side effects in the magnesium group were flushing and dizziness during and shortly after the 4-hour infusion. One patient experienced a vasovagal reaction and one patient reported palpitations. Two patients who received placebo reported palpitations. In both the placebo and the intervention group, pain in the vicinity of the insertion site of the intravenous cannula was reported: one patient receiving $MgSO_4$ developed phlebitis and one patient receiving placebo developed spreading pain around the cannula. During the off-label period, one patient experienced bradycardia leading to vasovagal collapse, and was subsequently shortly admitted to the hospital for observation.

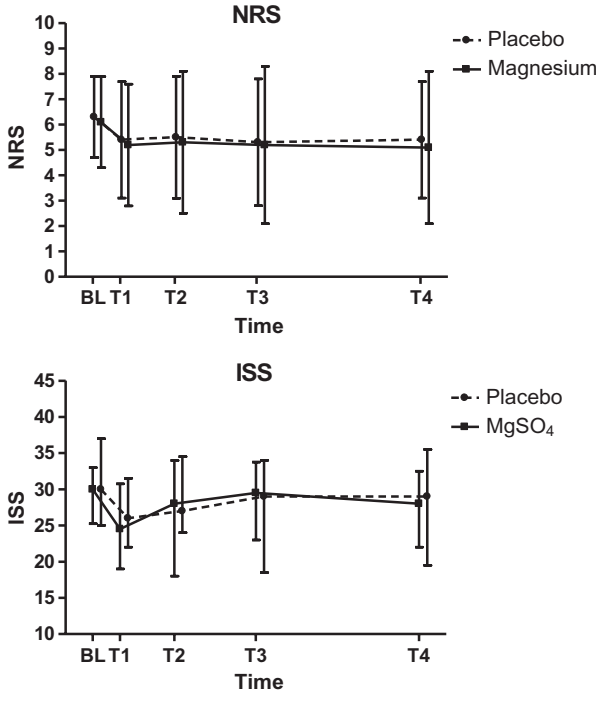

Figure 2 Pain scores (numerical rating scale [NRS]) and impairment level sum score (ISS) over time (mean and standard deviation [SD]).

Blinding

Blinding was evaluated in all 56 patients by asking researcher and patients what treatment they thought they received. In 17 cases, patients did not know what treatment they received (30%), 10 patients who received placebo were correct in their assumptions (37%), and 16 patients who had received $MgSO_4$ were correct (55%). Researchers were correct for patients that received placebo treatment in 17 cases (63%) and in 23 patients that received $MgSO_4$ (79%). Evaluations on assumption of either the patient or the researcher showed no significant difference for correct or incorrect assessment (Sign Test: $P = 0.58$ and $P = 0.45$, respectively).

Discussion

The results of this trial show a decrease of pain in the magnesium group as well as the placebo group, comparable to the changes observed in the off-label phase of the study. Although this change is statistically significant, 1 point improvement should not be considered clinically relevant. A statistically significant and clinically relevant improvement was observed for the ISS at the end of the intervention period and the McGill Pain scale (NWCt) up to 6 weeks follow-up in the magnesium group, which differed significantly from placebo at 1 week, mostly related to differences in the sensory subscale. This outcome suggests that sensory aspects of CRPS are influenced by magnesium. Although this measurement is clinically not relevant, it may strengthen the hypothesis about the effects of magnesium on sensory aspects in neuropathic pain. Job participation and EuroQol improved in the patient group treated with $MgSO_4$. Patients with low HADS in the magnesium group improved significantly more than patients with high scores on the HADS in this group.

The results of this study parallel those of the pilot study performed by our group [6], but the magnitude of the

Table 3 Impairment level sum score (total and subscores)

	Baseline (T0)			T1			T2			T3			T4		
	All	Placebo	$MgSO_4$	All	Placebo	$MgSO_4$	All	Placebo	$MgSO_4$	All	Placebo	$MgSO_4$	All	Placebo	$MgSO_4$
ISStot	30 (25–33)	30 (25–37)	30 (25.25–33)	25** (21–31)	26* (22–31.5)	24.5** (19–30.75)	27* (22.75–34)	27 (24–34.5)	28 (18–34)	29* (22–33.5)	29* (18.5–34)	29.5 (23–33.75)	28* (20–34.25)	29* (19.5–35.5)	28 (22–32.5)
	N = 55	N = 27	N = 28	N = 53	N = 25	N = 25	N = 50	N = 25	N = 25	N = 49	N = 25	N = 25	N = 50	N = 25	N = 25
ISSMcGill	6 (6–8)	6 (6–8)	6 (5–8)	5* (4–8)	6 (5–9.5)	5*† (3.25–6.75)	6* (4–9)	6 (4.75–9)	5.5* (3.5–7)	6* (3–8)	6* (3.5–8)	5* (3.5–7)	6 (4–8)	7 (4.5–8.5)	6 (3.5–7.5)
	N = 55	N = 27	N = 28	N = 53	N = 25	N = 28	N = 51	N = 26	N = 25	N = 49	N = 25	N = 24	N = 50	N = 25	N = 25
ISSBOX	8 (7–8)	8 (7–8)	8 (7–8.5)	7* (4–8)	6* (3.75–8)	7* (4.25–8)	7* (6–8)	7* (6–8)	7* (5.25–8.75)	8* (5–9)	8* (5.5–8)	7.5 (4.25–9)	8* (5–9)	7.5* (5–8)	8 (6–9)
	N = 56	N = 27	N = 29	N = 54	N = 26	N = 28	N = 54	N = 26	N = 28	N = 51	N = 25	N = 26	N = 55	N = 27	N = 28
ISSTEMP	5 (2–10)	5 (3–10)	5 (2–10)	4 (1–8)	4 (1–9)	3.5* (1.25–5)	5 (1–10)	4.5 (2–10)	5 (1–10)	5 (2–9)	5 (1.5–9)	4.5 (2–10)	5 (2–10)	6 (2–9)	5 (2–10)
	N = 56	N = 27	N = 29	N = 54	N = 26	N = 28	N = 54	N = 26	N = 28	N = 51	N = 25	N = 26	N = 55	N = 27	N = 28
ISSVOL	3 (1–6)	3 (1–7)	2 (1–5.5)	2 (1–5)	3 (1–5.25)	1 (1–4.75)	2 (1–4)	2.5 (1–4)	1 (1–3)	3 (1–6)	3 (1–5.5)	2.5 (1–6)	2 (1–4)	2 (1–4)	1 (1–3)
	N = 56	N = 27	N = 29	N = 54	N = 26	N = 28	N = 54	N = 26	N = 28	N = 51	N = 25	N = 26	N = 55	N = 27	N = 28
ISSAROM	7 (5–8)	7 (6–8)	6 (5–8)	6* (4–7)	6* (5–7)	5* (4–7.75)	6 (5–8)	6.5 (5.75–7.25)	6 (5–8)	6 (5–8)	6* (5–8)	6.5 (4.75–8)	6* (4–8)	6* (4–8)	5.5 (4–7.75)
	N = 56	N = 27	N = 29	N = 54	N = 26	N = 28	N = 54	N = 26	N = 28	N = 51	N = 25	N = 26	N = 55	N = 27	N = 28

ISS Median and IQR, * Significant difference to baseline ($P < 0.05$).
** Significant and relevant improvement (SSNtot change > 5) compared with baseline ($P < 0.05$).
† Significant difference between intervention and placebo group.

Table 4 Baseline McGill pain questionnaire values and median changes at baseline, T1, T2, T3, T4

	Baseline (T0)		T1		T2		T3		T4	
	Placebo N = 27	$MgSO_4$ N = 28	Placebo N = 26	$MgSO_4$ N = 28	Placebo N = 26	$MgSO_4$ N = 26	Placebo N = 26	$MgSO_4$ N = 25	Placebo N = 25	$MgSO_4$ N = 25
NWCt	12 (11–16)	12 (9–16)	11.5 (9.75–17.50)	9*# (6.25–12.75)	13 (8.75–17.25)	10.5* (6.75–13.25)	12* (7.50–15)	10* (5.5–14)	13 (8.5–16.5)	11 (6.25–15.25)
NWCsen	8 (6–10)	7 (6–10)	7.5 (6–11)	6*# (4–8)	8 (5–11)	6 (4–9)	7 (5.75–9.25)	5* (4–9)	8 (5.5–10.5)	5.5 (5–9.75)
NWCaff	2 (1–4)	2 (1–4.75)	1.5 (1–5)	1* (0.75–3.25)	2 (1–4.25)	1* (0.75–3.25)	1.5* (0.75–3.25)	2 (0.5–3)	2 (1–4)	2 (1–3.75)
NWCev	3 (2–3)	3 (2–3)	3 (2–3)	2*# (1–3)	3 (2–3)	3 (1–3)	3 (2–3)	3* (1–3)	3 (2.5–3)	3 (1–3)
PRIt	25 (19–29)	22.5 (16.25–30.25)	21.5* (12.75–28.25)	16.5* (9.25–21)	21.5* (11.75–27)	20* (9.5–26)	19* (12–26.75)	17* (10–28)	22 (13.5–29)	18.5 (10.5–32)
PRIsen	15 (12–18)	13 (9.25–19.75)	11* (8–17.25)	9* (6–14.25)	13* (7–16.25)	11.5* (6–15.25)	12* (8–17.5)	9 (6–16.5)	13 (8.5–18.5)	11 (8–19)
PRIaff	3 (1–6)	3.5 (1–5)	2 (1–5.25)	2* (0.25–4.75)	2.5 (1–5)	1.5* (0.75–5.25)	2 (0.75–4.25)	2* (0.5–5)	2 (1–5)	2 (1.25–5)
PRIev	6 (5–8)	5 (4–7)	5 (3–6.5)	4* (2–5.75)	5* (3–6.25)	5 (2.75–8)	5* (3–7.25)	4* (2.5–7)	5 (4–7.5)	5 (2–8)

Data in median and interquartile range (Wilcoxon and Mann–Whitney analysis). Shaded portions of the table represent relevant findings of the trial.
* Significant improvement compared with T0 ($P < 0.05$).
# Significant difference compared with placebo ($P < 0.05$).

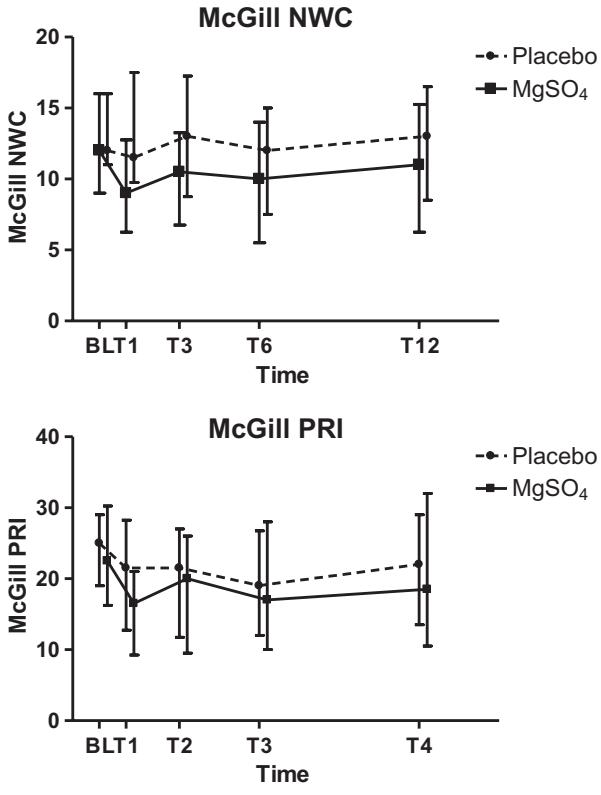

Figure 3 Changes on McGill: number of words counted (NWC) and pain rating index (PRI) (median and interquartile range [IQR]).

effects are substantially smaller. The difference in the studied population between the present trial and the pilot study concerning disease duration and inflammatory profile may have resulted in differences in effect sizes. Patients with a shorter disease duration as included in the pilot study are generally more likely to respond positively to interventions [42], and the prognosis of spontaneous improvement is better in CRPS-1 patients with shorter disease duration. Differential effects of magnesium for patients with a shorter disease duration compared with chronic patients may be expected as a consequence of the activity of the NMDA receptor during the cascade leading to central sensitization. Reduction of the activation of NMDA receptors in an early stage can possibly prevent or counter the still relatively limited process of central sensitization and therefore prevent more substantial changes found in the dorsal horn and the cortex in later phases of CRPS [3,43,44]. As exaggerated inflammation has been proposed to play a role in the initial stages of CRPS-1 development. The direct properties of magnesium as an anti-inflammatory agent may play a role in differences of outcome between the pilot study and the present trial. Treatment with $MgSO_4$ has been shown to inhibit the release of inflammatory molecules [45,46] including TNFα and nuclear factor-$\kappa\beta$, which are related to the development of CRPS [47,48]. In addition, for both the

Table 5 Sensibility measured by Semmes Weinstein filaments

	Baseline		T1		T2		T3		T4	
	Affected	Non-aff.	Affected	Non-aff.	Affected	Non-aff.	Affected	Non-aff.	Affected	Non-aff.
All (N = 54)	3.66	4.25	3.61	3.88	3.64	4.16	3.53	3.94	3.79	4.08
Placebo (N = 27)	3.98	4.09	3.53	3.56	3.67	3.64	3.51	3.57	3.61	3.72
$MgSO_4$ (N = 27)	3.64	4.36	3.67	3.70	3.57	4.36	3.63	4.06	3.81	3.76
Upper extremity (N = 16)	3.19	3.22	3.29	3.22	3.35	3.19	3.22	3.22	3.30	3.18
Placebo (N = 10)	3.15	3.16	3.22	3.16	3.15	3.16	3.30	3.22	3.29	3.06
$MgSO_4$ (N = 6)	3.42	3.29	3.30	3.35	3.35	3.19	3.16	3.22	3.19	3.32
Lower extremity (N = 38)	4.40	4.77	4.21	3.89	4.42	4.57	4.49	4.16	4.51	4.23
Placebo (N = 17)	4.56	4.94	3.85	3.78	4.21	4.56	3.61	4.04	4.20	4.20
$MgSO_4$ (N = 21)	3.98	4.51	4.16	3.94	3.99	4.67	4.47	4.24	4.17	4.25

Median and interquartile range (IQR) of sensed monofilament of the affected and the nonaffected extremity (used filaments from thinnest to thickest: 1.65, 2.83, 3.22, 3.61, 3.84, 4.08, 4.31, 4.56, 6.65) (measures are related from the mean felt monofilament of the five tested locations).

Table 6 Patient characteristics off-label study

	Total
N	16
Female/male	15/1
Age (years)*	46.1 (12.7)
Duration (months)†	9.5 (4.25–19.25)
Upper/lower	5/11
Right/left	7/9
Initial trauma	
Fracture	4
Soft tissue injury	4
Operation	4
Nerve-related operation	1
Spontaneous	1
Wound	0
Other traumas	2
Initial temperature	
Warm	3
Cold	5
Alternating	3
Unknown	4
Mean NRS baseline*	6.6 (1.5)

* Mean (standard deviation [SD]).
† median (interquartile range [IQR]).

pilot and the present study, the effects of standardized adjuvant physical therapy may have contributed to improvement in pain and impairment [23]; however, a placebo effect cannot be ruled out.

Studies focusing on the NMDA receptor antagonist ketamine for CRPS show much more pronounced effects on pain compared with those found in the present study. Ketamine as a noncompetitive NMDA receptor antagonist inhibits NMDA signaling by interacting with phencyclidine-binding sites and receptors on membrane associated sites, whereas magnesium, a competitive NMDA receptor antagonist, blocks the calcium channel to reduce calcium influx [49]. The difference in pharmacotherapeutic profile of both substances relates to the higher potency of ketamine as an NMDA receptor antagonist. Effects observed in the present study appear to be time limited, which was also observed for ketamine in the study by Sigtermans et al. [7]. The limited duration of these effect suggests that permanently reversing the process of central sensitization and maladaptive neural plasticity is not achieved and that the effect may be related to short-term analgesic effects of the NMDA receptor antagonists [2]. The strong analgesic potency of ketamine is known as it is used in surgical settings.

We hypothesize that on one hand the severity and the duration of the inflammation relates to the probability of sustained maladaptive neuroplastic changes, while continuous activation may lead to irreversible changes in peripheral and central NMDA receptors. On the other hand, differences in the intrasynaptic environment of the NMDA receptor between individuals concerning availability of calcium, magnesium, or inflammatory mediators influencing NMDA receptor phosphorylization and activation should be considered. In this context, measurement of the biological availability of magnesium to assess the predictive value of possible deficiencies in the development of central sensitization in CRPS-1 may be warranted.

In order to understand the mechanism of central sensitization, changes of the NMDA receptors and associated neuroplastic changes in CRPS-1 fundamental research are needed. Studies focusing on histological changes or spreading of the NMDA receptors may also lead to a better understanding of the role of central sensitization and the NMDA receptor in CRPS [4].

Some limitation with regard to the present study has to be addressed. The heterogeneity of patients with CRPS, in general and consequently in our trial, is a challenging aspect in CRPS research. The primary focus of this study was to target aspects of central sensitization in CRPS-1. However, the patients included in this study differed with regard to spectrum and severity of features of central sensitization, therewith contributing to between subject variance. Furthermore the long disease duration and a predominantly cold-affected extremity may have contributed to the lack of efficacy found in this study. The fact that the placebo group had a shorter disease duration at baseline may have contributed to the lack of difference found between interventions in this study. Inclusion of patients with a clinical profile more favorable to respond to magnesium may have led to other results than found in this study. Heterogeneity of the patient population may be limited by using the current Budapest criteria (clinical or research), which have been validated in 2010 and have a higher specificity and sensitivity for diagnosing CRPS. Objective outcome measurements in studies on CRPS are challenging. In this study, it was decided to use the validated ISS as primary outcome measure; however, limitations of this measurement tool are the standardized measurements on temperature (limited to five locations) and range of motion (limited to chosen joints). This may have under- or overestimated the disease severity in individual patients. Improvement of objective measurement tools for impairment in CRPS can be considered in future research. Furthermore, inclusion of patients for this study proved difficult, whereby only 25% of the eligible patients agreed to participate. As a consequence, the number of included patients fell short of the number required in the power analysis (i.e., 56 as opposed to 66). However, reaching a significant difference between magnesium and placebo would have been highly unlikely considering the very small difference between both interventions for the evaluated patients (i.e., 0.3 point on the BOX-11 at 12 weeks).

Conclusions

Intravenous administration of magnesium as used in our study has no additional benefit over placebo in treatment of CRPS-1 in chronic CRPS-1. Studies involving selected

groups of CRPS-1 patients with shorter disease duration, a florid inflammatory profile, or severe signs and symptoms of sensitization are required in order to assess magnesium for its additional value to available treatment methods for CRPS-1.

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Author Contributions and Conflict of Interest

All authors contributed substantially to this manuscript and declare no conflict of interest.

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