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Original Article

A double-blinded randomised controlled study of the value of sequential intravenous and oral magnesium therapy in patients with chronic low back pain with a neuropathic component

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Summary

Persistent mechanical irritation of the nerve root sets up a series of events mediating sensitisation of the dorsal roots and dorsal horns in the spinal cord. Current evidence supports the role of magnesium in blocking central sensitisation through its effect on *N*-methyl–D-aspartate receptors. We studied the role of sequential intravenous and oral magnesium infusion in patients with chronic low back pain with a neuropathic component. We recruited a cohort of 80 patients with chronic low back pain with a Leeds Assessment of Neuropathic Signs and Symptoms pain scale score $\geq$ 12, who were receiving a physical therapy programme. All patients were treated with anticonvulsants, antidepressants and simple analgesics; in addition 40 patients received placebo for 6 weeks (control group), while the other 40 patients received an intravenous magnesium infusion for 2 weeks followed by oral magnesium capsules for another 4 weeks (magnesium group). Patients were asked to rate their pain using a numerical rating scale. Lumbar spine range of motion was also determined using a long-arm goniometer. In the magnesium group, the patients' numerical rating scales revealed a significant reduction in pain intensity. The mean (SD) pre-treatment value was 7.5 (2.2) compared with 4.7 (1.8) at 6 months ($p = 0.034$). The reduction in pain intensity was accompanied by significant improvement in lumbar spine range of motion during the follow-up period. The mean (SD) values of flexion, extension and lateral flexion movements before treatment and at 6-month follow up were 22.2 (8.4) vs 34.7 (11.5) ($p = 0.018$), 11.8 (3.4) vs 16.9 (3.5) ($p = 0.039$), 11.4 (3.6) vs 17.2 (4.4) ($p = 0.035$), respectively. Our findings show that a 2-week intravenous magnesium infusion followed by 4 weeks of oral magnesium supplementation can reduce pain intensity and improve lumbar spine mobility during a 6-month period in patients with refractory chronic low back pain with a neuropathic component.

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In many countries chronic, low back pain is the most common cause of long-term disability in middle age and should be considered a major public health problem. It is the second most common cause for lost workdays and activity limitation among those under age 45 years, affecting sufferers' abilities to work, sleep and perform other activities essential to leading a full life [1, 2].

Chronic low back pain with a neuropathic component is a challenging pathology, caused mostly by a variety of lesions of nociceptive sprouts within the degenerated disc, mechanical compression of the nerve root, or as a result of inflammatory mediators originating from the degenerative disc [3].

Pharmacotherapy for neuropathic pain includes the use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, but with variable responses [4]. Anticonvulsants and tricyclic antidepressants may be of benefit due to their pain-modulating effects [5, 6]. Unfortunately, these treatment modalities fail many patients. Thus, there is an unmet clinical need and a challenge to develop more effective therapy. When drugs such as anticonvulsants or antidepressants fail to provide satisfactory analgesia for patients with chronic pain, other drugs such as *N*-methyl-D-aspartate (NMDA)-receptor antagonists may provide a suitable option [7].

The NMDA receptor has a vital role in the pathogenesis of central sensitisation or wind-up in the spinal cord and is subsequently essential for the establishment of chronic neuropathic pain states. The high incidence of psychomimetic adverse effects from ketamine [8] and the beneficial effect of other NMDA-receptor antagonists in patients with chronic back pain motivated us to seek other alternative therapies such as magnesium [9].

Physiologically, magnesium has been demonstrated to block the ion channel on the NMDA receptor, thus preventing extracellular calcium ions from entering the cell, leading to secondary neuronal changes. This mechanism could prevent nociceptive-associated central sensitisation and lessen the increased activity of wide dynamic range neurons in the dorsal horn after prolonged stimulation [10]. We therefore evaluated the therapeutic role of sequential intravenous and oral magnesium therapies in patients with chronic low back pain with a neuropathic component.

Methods

Our study was approved by an Investigational Review Board of the Faculty of Medicine of Tanta University. Written informed consent was obtained from patients participating in the study.

We recruited 80 patients suffering from chronic low back pain with a neuropathic component, a Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) pain scale score $\geq$ 12, with or without leg pain for more than 6 months' duration attributed to specific neurological findings, and with inadequate pain relief from conventional treatment, i.e. antidepressant and anticonvulsant drugs, as well as opioids, paracetamol and NSAIDs. Each patient was assigned to one of the two study groups.

We did not study patients with acute low back pain or chronic low back pain of non-neuropathic nature (LANSS pain scale < 12), spine-related musculoskeletal pain, and those with contraindications to magnesium therapy such as known magnesium hypersensitivity, impaired renal function, cardiac conductance disturbances, congestive heart failure, severe liver disease and respiratory disease.

All patients were evaluated for age, sex, height, weight, body mass index, duration of pain in months, physical examination, medical and surgical history, level of neuronal dysfunction (determined according to clinical examination) and radiological investigations including computerised tomography and magnetic resonance imaging scans. The LANSS pain scale was used to discriminate between neuropathic and nociceptive pain. The LANNS assessment score was performed under calm conditions by the same pain physician who was blinded to the study design, and who did not participate in the study or data collection at the time of the patient's first visit to the pain clinic. For each patient in whom allodynia and hyperalgesia were present, sensory function of the overlying skin was compared with that at a non-painful control site, usually at a similar site on the contralateral side.

The LANSS pain scale consists of two parts: a five-item questionnaire on the nature of the pain that has to be completed by the patient; and a simple sensory testing component to assess for the presence of allodynia and hyperalgesia. A LANSS scale pain score $\geq$ 12 implies that neuropathic pain is most probably present. Mechanical allodynia was assessed by gently stroking the skin area with a piece of cotton wool. Ethyl chloride spray was used to assess for cold allodynia. Hyperalgesia was assessed using a pinprick test [11].

The recruited patients continued with their previous medications until their commencement in the study, at which point all prior medications and therapies were discontinued and only the study drugs were administered.

All patients received gabapentin 300 mg orally three times daily, amitriptyline hydrochloride 25 mg orally at bedtime, and, celecoxib 200 mg orally twice daily. These were packaged in specific bottles labelled 1, 2 and 3 to reflect the morning, afternoon and night time doses, respectively. The 40 patients in the treatment (magnesium) group received an intravenous infusion of magnesium sulphate 1 g in 250 ml saline 0.9% with its label removed and relabelled with 'MG'. This was given over 4 h every day for 2 weeks. After 2 weeks, the infusion was replaced by oral magnesium therapy twice daily for 4 weeks using capsules containing magnesium oxide 400 mg and magnesium gluconate 100 mg. These capsules were packaged in group-specific bottles labelled 'MG'. The 40 patients in the control group received an intravenous infusion of 250 ml saline 0.9% (with its label removed and relabelled 'CG'), followed by placebo sugar-filled capsules identical in shape and colour to the magnesium capsules, which were packaged in group-specific bottles labelled 'CG'. The control group placebo drugs were administered using the same dosing schedule as the magnesium group.

Only the hospital pharmacist who prepared the drugs was aware of the label meanings, which were disclosed only after completion of the study. Of note, most of the recruited patients were illiterate of a foreign language.

Randomisation was performed using a sealed envelope technique without sex stratification. The randomisation envelopes, drug bottles and their coded labels were prepared by the hospital pharmacy with a pain physician who was independent of the study. The magnesium infusion was administered on an outpatient basis under the supervision of a pain specialist. The patients' physiological parameters were monitored using continuous ECG, pulse oximetry, and non-invasive blood pressure every 15 min.

Both patients and medical assessors were blinded to the study protocol. A physician who was independent of the study read the number contained in the envelope and made group assignments. Participants and pain clinic nurses administering the drugs were blinded to the group assignment.

Based on previously published safety data for magnesium therapy in similar doses to those used in our study [12, 13], and the fact that measurement of serum magnesium concentration does not represent tissue magnesium content [14], we did not measure the serum magnesium levels of our enrolled patients during the study period.

All patients received interferential current therapy (IFC) using four electrodes of two circuits arranged in a cross. A frequency of 70 Hz was applied for three 20-min sessions every week. In addition, back muscle strengthening exercises were undertaken on alternate days throughout the study period.

Patients were asked to rate their pain intensity by an independent pain physician using a 11-point numeric scale (NRS) ranging from 0 to 10. The same pain physician performed the NRS for each patient during their follow-up visits.

As a secondary outcome measure, the patients' lumbar spine range of movement was determined using a long-arm goniometer. An independent, blinded physiotherapist undertook measurements of flexion, extension and lateral flexion. The same physiotherapist performed the repeat measurements for each patient during his follow-up visits.

Side-effects were assessed by an independent pain physician using direct questioning and spontaneous reporting during the intravenous infusion phase of the study.

We calculated that we would need 30 patients per group to have an 80% chance of detecting a 35% reduction in NRS at a 5% significance level, using a Mann–Whitney test with a 0.05 two-sided significance level and allowing for a 10% attrition/non-compliance rate (nQuery Advisor, Version 5.0; Statistical Solutions, Saugus, MA, USA). To enable detection of potential differences in the side-effects between the two groups, we recruited 40 patients to each group.

Statistical analyses included the chi-squared test for differences in proportions, and two-way ANOVA to test for multiple comparisons with respect to pre- and post-treatment results for pain scores and lumbar spine ranges of movement.

Results

We recruited 80 patients into the study. Patients' characteristics were similar between the two groups (Table 1). The drugs and doses were well tolerated by all patients and were continued throughout the study period.

All patients reported a statistically significant reduction in pain intensity at 2 weeks. In the magnesium group only, this reduction continued throughout the 6-month follow-up period, with mean (SD) pre-treatment NRS values of 7.5 (2.2) compared with 4.7 (1.8) at 6 months (Table 2).

All patients experienced statistically significant improvements in their lumbar spine ranges of movement at the 2-week point. However, this improvement persisted only in the magnesium group in whom it improved throughout the 6-month study period (Table 3).

Overall, the side-effects of the magnesium therapy were minimal, with four patients reporting mild diarrhoea during their oral magnesium treatment; this did not necessitate discontinuation of their therapy.

Discussion

To the best of our knowledge, this study is the first to examine the effects of long-term magnesium therapy in patients with refractory chronic back of a neuropathic nature. Our results indicate that the regimen of magnesium and physical therapy provided to patients in the study (magnesium) arm produced a significant reduction in their pain intensity and significant improvements in all ranges of their lumbar spine mobility for the duration of the 6-month follow-up period when compared with both baseline and control group values.

Chronic low back pain is often severe, persistent and incapacitating and is frequently resistant to conventional treatments; as a result, patients can suffer severe long-term disability [15]. Persistent and repetitive stimulation of C-fibres can lead to a prolonged and amplified pain response (the 'wind-up' phenomenon), which occurs as a result of NMDA-receptor activation. Under normal physiological conditions, the ion channels of these receptors are blocked by magnesium ions (Mg^{2+}) found in the neuronal tissues. This unique channel blockade by Mg^{2+} requires a sustained depolarisation of the membrane to allow the NMDA-receptor channel to be re-activated and opened. *N*-methyl-D-aspartate receptor activation has been clearly shown to play a key role in the hyperalgesia and enhancement of pain signalling (central sensitisation) seen in persistent pain states with a neuropathic

Table 1 Characteristics of patients with chronic low back pain in the control and magnesium groups. Values are mean (SD) or number (proportion).

	Control (n = 40)	Magnesium (n = 40)	p value
Age; years	57.8 (12.3)	55.1 (14. 8)	0.69
Sex			
Male	28 (70%)	25 (62.5%)	0.74
Female	12 (30%)	15 (37.5%)	
Weight; kg	95.7 (15.4)	93.9 (12.5)	0.64
Height; cm	165 (15.8)	169 (14.8)	0.42
LANSS pain scale	16 (2)	18 (2.5)	0.52
Duration of pain; months	7.9 (1.9)	8.5 (2.1)	0.32
Level of neuronal dysfunction			
L3–4	9 (22.5%)	10 (25%)	0.42
L4–5	22 (55%)	19 (47.5%)	0.51
L5–S1	9 (22.5%)	11 (27.5%)	0.17
Patients with leg pain	32 (80%)	30 (75%)	0.45
Patients receiving oral opioids			
Tramadol; 50 mg.12 h^{-1}	25 (62%)	22 (55%)	0.18
Morphine sustained release tablets; 30 mg.12 h^{-1}	9 (22.5%)	10 (25%)	0.15

LANSS, Leeds Assessment of Neuropathic Signs and Symptoms.

Table 2 Comparison of Numeric Rating Scale pain scores for patients in the control and magnesium groups. Values are mean (SD).

			p value		
	Control	Magnesium	Between groups	Within control group	Within magnesium group
Pre-treatment	7.4 (2.4)	7.5 (2.2)	0.62		
2 weeks	3.6 (1.4)	3.4 (1.15)	0.28	0.036	0.022
6 weeks	6.6 (1.7)	3.9 (1.4)	0.003	0.26	0.029
3 months	6.8 (2.2)	4.4 (1.6)	0.045	0.51	0.016
6 months	7.2 (2.45)	4.7 (1.8)	0.027	0.25	0.034

Table 3 Comparison of range of motion of lumbar spine in chronic low back pain patients in control and magnesium (Mg^{2+}) groups. Values are mean (SD).

	Flexion (°)*		Extension (°)*		Lateral flexion (°)*		p value†		
	Control	Mg^{2+}	Control	Mg^{2+}	Control	Mg^{2+}	Flexion	Extension	Lateral flexion
Pre-treatment	23.7 (7.3)	22.2 (8.4)	12.8 (3.3)	11.8 (3.4)	11.4 (3.6)	10.9 (3.9)	0.25	0.36	0.28
2 weeks	35.6 (9.7)	38.7 (10.9)	18.7 (3.5)	19.8 (4.4)	19.2 (3.6)	19.8 (3.1)	0.55 0.039/0.026	0.29 0.034/0.015	0.35 0.017/0.021
6 weeks	28.5 (7.4)	36.9 (12.0)	12.7 (3.6)	18.6 (3.7)	12.6 (3.7)	18.5 (3.3)	0.042 0.27/0.015	0.038 0.64/0.022	0.023 0.38/0.025
3 months	26.8 (8.2)	35.8 (11.2)	12.8 (4.8)	18.2 (4.2)	12.5 (3.9)	18.3 (3.9)	0.034 0.46/0.025	0.04 0.48/0.026	0.037 0.42/0.014
6 months	25.6 (8.5)	34.7 (11.5)	11.7 (3.6)	16.9 (3.5)	11.2 (3.6)	17.2 (4.4)	0.021 0.62/0.018	0.046 0.55/0.039	0.028 0.33/0.035

*Normal flexion = 50°; normal extension and lateral flexion = 25°.
†Single p values refer to comparisons between groups; 'double' p values refer to comparisons within groups (control/magnesium, respectively, compared with pre-treatment values).

component. Central sensitisation of spinal neurons and higher structures of the nervous system is one of the causes of pain intensification and is responsible for the chronic character of pain, which is clinically manifest as hyperalgesia and allodynia [16].

The main mechanism by which the NMDA receptor acts is through the large influx of calcium ions (Ca^{2+}) when the channel is activated. Once inside the cell, Ca^{2+} can activate various effectors and promote downstream changes that can themselves promote mechanisms of plasticity and long-term potentiation. Therefore, the targeting of NMDA receptors by pharmacological means has been explored in depth as an analgesic strategy [15].

Different rehabilitation programmes can be used in combination to produce improvements in pain and functional restoration for patients with disabling chronic low back pain [17]. Most rehabilitation programmes consist of active physical treatment, a cognitive-behavioural treatment and a combination of both. The use of these three theory-based treatments has been shown to be more effective than non-treatment in patients with chronic low back pain. Active physical treatment and cognitive-behavioural treatment alone are as effective in improving the level of patient function as combination treatment. However, after long-term follow up with cost effectiveness analysis, active physical treatment seems to be the most beneficial option [18].

A number of mechanisms have been proposed for the anti-nociceptive effects of magnesium, including the inhibition of intracellular calcium influx (calcium channel blockers augment morphine-induced analgesia and decrease total opioid consumption), antagonism of NMDA receptors, and the prevention of enhanced ligand-induced NMDA signalling seen in the presence of hypomagnesaemia [19–21]. In addition, magnesium

seems to attenuate or even prevent central sensitisation after peripheral tissue injury or inflammation because of inhibition of dorsal horn NMDA receptors [9, 22, 23].

Several studies have reported the anti-nociceptive effects of intravenous magnesium, suggesting that the use of magnesium as an NMDA-receptor antagonist can reduce neuropathic pain. Begon et al. [7] concluded that magnesium amplifies the analgesic effect of low-dose morphine in conditions of sustained pain, and that magnesium may have a clinical application in patients with neuropathic and persistent types of pain. Koinig et al. [22] concluded that the administration of magnesium sulphate led to a significant reduction in intra- and postoperative fentanyl requirements in patients undergoing arthroscopic knee surgery under total intravenous anaesthesia. In addition, Tramer et al. [23] concluded that peri-operative administration of magnesium sulphate was associated with lower analgesia requirements and better quality of sleep. Hwang et al. [24] and Apan et al. [25] concluded that magnesium sulphate given intravenous during spinal anaesthesia reduced postoperative pain and analgesic consumption without complications.

Grosby et al. [12] demonstrated that intravenous magnesium infusion in patients with cancer led to partial or total relief from neuropathic pain that had been poorly responsive to opioids. Magnesium is a relatively cheap drug that is readily available in both injectable and oral forms; it is easy to use in clinical practice and presents a beneficial cost-benefit ratio when used in patients with refractory neuropathic pain.

We believe that the use of magnesium presents a viable treatment option for patients with refractory chronic back pain who have failed to respond to conventional treatment. Further studies are needed to identify the optimum period of treatment, optimum dose, and potential benefit of combining magnesium use with other NMDA antagonists when managing patients with different forms of neuropathy.

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Competing interests

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