Oral magnesium treatment in patients with neuropathic pain: a randomized clinical trial

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Abstract. Studies in animals and in patients have suggested that magnesium (Mg), a physiological blocker of N-methyl-D-aspartate receptor, could have an antinociceptive effect in painful situations. This randomised, double-blind, controlled trial in two parallel groups aims at studying oral Mg effects in patients with neuropathic pain. It explores the impact of Mg (6x419 mg Mg chloride/capsule per day for a month), versus placebo (lactose) on pain [Neuropathic Pain Symptom Inventory (NPSI) and numerical scale (NS)], and on quality of life indicators after 4 weeks treatment, in 45 patients suffering from neuropathic pain. After 4 weeks, NPSI, NS and quality of life are not different in the Mg and placebo groups, while the frequency of pain paroxysms diminishes and the emotional component improves in the Mg group compared to baseline. This clinical trial displays a large placebo response and could not demonstrate any significant difference in pain alleviation after a month of oral treatment between Mg and placebo in patients suffering from neuropathic pain. Frequency of pain paroxysms and emotional impact will be explored in future studies as they constitute major aspects of pain alleviation in chronic pain conditions.

Key words: neuropathy, quality of life, placebo, pain paroxysm, emotion

Among the mechanisms underlying neuropathic pain, N-Methyl-D-Aspartate (NMDA) receptors have been shown to play a central role in the generation and maintenance of spinal hypersensitivity phenomenon leading to chronic pain [1-4]. NMDA receptors are ubiquitous receptors and are not only involved in the establishment of central sensitization [5] and in synaptic plasticity but also in many pathophysiological processes such as memory, learning and neurological disorders [6]. Magnesium (Mg2+) is a physiological blocker of the Na+/Ca2+ channel of the receptor and is able to modulate NMDA receptor activation [7]. NMDA receptor antagonists have been shown to diminish pain in animal models of neuropathic pain [8, 9] or inflammatory pain [10]. Despite their well-established clinical efficacy [11], the use of NMDA antagonists like ketamine is very limited because of the high occurrence of adverse effects [12]. Conversely, Mg2+ has very few side-effects and systemic treatment with multiple doses of magnesium in diabetic and mononeuropathic rats could reverse mechanical hyperalgesia [1]. Likewise, intrathecal administration of Mg2+ has shown antinociceptive effects on neuropathic [13] and...
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inflammatory pain [14, 15]. Furthermore, Mg$^{2+}$-deficient rats develop a mechanical hyperalgesia [16-18], whereas the addition of intraperitoneal or intrathecal Mg$^{2+}$ sulphate attenuates neuropathic pain [3, 19]. The suppression of neuropathic pain may be partially a result of the enhanced blocking of NMDA receptors by the increased magnesium in NMDA receptorgated ion channels [20]. In clinical settings, several studies have demonstrated the effectiveness of magnesium on pain and also on quality of life [21-23] mainly in pre and post-surgery periods [24-29], with contradictory results showing that Mg$^{2+}$ did not always significantly decrease the postoperative morphine requirement [24].

Very few clinical studies have focused on the efficacy of Mg$^{2+}$ in neuropathic pain [30-32]. Tanaka et al. [32] observed in 8 patients with postherpetic neuralgia or causalgia, that repetition of magnesium administration once a week decreased the pain visual analog scale score after a few weeks of treatment, with no side effects. Brill et al., 2002 [30] showed, in 7 patients with postherpetic neuralgia, in a double-blind placebo-controlled, cross-over study, a significant diminution of pain 30 min after intravenous (IV) Mg$^{2+}$ sulphate (30 mg/kg) with no side-effects. Felsby et al., 1996 [31] showed, in 10 patients with peripheral neuropathic pain, in a double-blind placebo-controlled, cross-over study, no change in pain and allodynia in patients receiving Mg (0.16 mmol/kg).

Pain and quality of life are tightly interrelated and several randomised trials have investigated the impact of magnesium on the quality of life of patients with pain [21, 23]. Mg is vital for the activity of more than 300 enzymes and plays an important role in neurochemical transmission [33]. Collins et al., 2009 [21] showed in patients with Complex Regional Pain Syndrome Type 1 that IV Mg$^{2+}$ (70 mg/kg) significantly improved pain and quality of life. Shechter et al., 2003 [23] have demonstrated in patients with coronary artery disease that oral magnesium supplementation (15 mmol twice daily) for 6 months improved exercise-induced chest pain, quality of life and exercise tolerance. Other studies have shown an involvement of magnesium in the quality of sleep and quality of life [22, 24].

The significant benefits of Mg supplementation in animals with neuropathic pain [1-3] have so far been little studied in outpatients suffering from neuropathic pain. The aim of this study was to evaluate for the first time in patients the effect of magnesium, taken orally at therapeutic doses, on neuropathic pain and on quality of life.

Material and methods

Study

This was a prospective, randomised, double-blind, controlled study, with two parallel groups of patients suffering from neuropathic pain. All included patients came from the Clinical Pharmacology Department of Clermont-Ferrand University Hospital (France) and were followed by the same medical team. The study received the agreement of the Ethics Committee and of the French Drug Agency, was declared on clinicaltrials.gov (NCT01121653) and followed standardized ethical and safety Good Clinical Practice Guidelines.

Patients

Inclusion criteria include neuropathic pain of post-herpetic, traumatic or surgical origin of more than one year duration. Exclusion criteria include central and diabetic neuropathic pain, a renal clearance of less than 30 mL/min, any Mg contraindication, Mg concentration outside the normal range [extracellular Mg (0.65 to 1.05 mmol/L), intracellular Mg (1.65 to 2.5 mmol/L)], quinidine intake, a change of treatment during the 2 weeks before randomisation and an evolutive pathology. On the selection visit, eligible patients were informed about the protocol and provide a signed informed consent. Blood samples for extra and intracellular concentrations of Mg, and for creatinine concentration were taken. A clinical exam, a neuropathic pain questionnaire: Neuropathic Pain Symptom Inventory (NPSI) [34], Hospital anxiety and depression scale (HAD) [35] and a quality of life questionnaire: MOS 36-Item Short Form Survey Instrument (SF36) [36] were carried out. The patient was then given a booklet for a daily auto-evaluation of pain intensity on a 0-10 numerical scale (NS), pain paroxysms and mention of any drug treatment for two weeks. Patients were included only if they were stable on their analgesic treatment which must have been taken for at least 21 days and which could not be modified until the end of the protocol. Patients
came back two weeks later to the Pharmacology Centre and were randomized if they were still eligible with a mean 24 hour-pain report over the last week of more than 3 out of 10. Patients were allocated to treatment A or B from the randomisation list that had been established by a clinical research assistant not involved in the protocol. Randomisation was by blocks of 4. Treatment A and B corresponded respectively to trihydrated Magnesium Chloride (Mg) 419 mg per capsule equivalent to 55 mg Mg2+ per capsule, or placebo (lactose), 6 tablets a day, two to be taken with every meal, and given to the patient by the medical investigator. The participants were then sent home with a similar booklet for a daily autoevaluation of pain intensity, pain paroxysms, and mention of any drug treatment, for at least 28 days and up to 31 days because of bank holiday week-ends. Collection of the booklets, clinical examination, blood sampling and questionnaires were repeated on the last visit (day 29 after randomization).

The main evaluation criterion was the comparison of the NPSI score between randomization and the end of the protocol. Secondary end-points were the changes in mean pain intensity [numerical scale NS (0 to 10)], maximal pain and the number of pain paroxysms between the week before starting the treatment (W-1) and the last week of treatment (W4), and scores of HAD and SF36 questionnaires.

**Questionnaires**

The Neuropathic Pain Symptom Inventory (NPSI) [34] is a validated self-questionnaire that allows with 10 descriptors the discrimination and quantification of five distinct clinically relevant dimensions of neuropathic pain and which is sensitive to the effects of treatment. It evaluates the symptoms of neuropathic pain and presents ten descriptors (Burning, Pressure, Squeezing, Electric shock, Stabbing, Evoked by brushing, Evoked by pressure, Evoked by cold stimuli, Pins and needles, Tingling) for 5 dimensions of pain (Burning, Squeezing, Paroxystic pain, Provoked pain, Paresthesia).

Hospital anxiety and depression scale (HAD) is a self screening questionnaire including 14 questions (7 for anxiety and 7 for depression) each rated from 0 to 3 with a total score of 21 each. 4 classes have been defined: 0-7 = normal, 8-10 = moderate, 11-14 = average, 15-21 = severe. Higher scores correspond to higher levels of anxiety and depression [35]. The SF36 (MOS 36-Item Short Form Survey Instrument) is the most widely used generic instrument for measuring health-related quality of life, and is frequently used in studies on headache [36].

**Statistics**

The trial used a parallel group design and interpatient comparison between the two treatments (placebo and magnesium) was based on primary endpoints. The standard deviation was estimated in a previous study to be 8, alpha risk was taken at 5% and beta risk at 10%. Based on these assumptions, with an expected difference in NPSI of 8 between D29 and D0, and with the possibility of a drop out of patients, a final sample size of 50 patients was calculated in order to have at least 42 analyzable patients at the end of the study.

The distribution of patient age, gender, weight, height between groups was checked by means of t test for continuous variables, or frequency comparisons. For all other parameters the analysis was carried out by means of Analysis of variance for continuous variables, or frequency comparisons. Analysis were carried out on all data when possible [factor, time, treatment and subject (treatment)], or by treatment to assess the time influence (D0 vs D29) or by time to assess the treatment influence (Placebo vs magnesium). Frequency comparisons were analyzed by means of Chi-square tests, using an Exact test method in order to estimate the exact two-sided \( P \)-value. Statistics were performed on SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) for Windows XP. Data are given as means ± SD.

**Results**

**Patient characteristics**

Fifty patients were included and the data of 45 patients were analysed (age=53±11 years, 23 women, 22 men; height 160±10 cm, weight 68±14 kg). 23 were allocated to placebo and 22 to magnesium (figure 1). 5 patients dropped out before
randomisation: 1 because of high magnesemia, 3 because of illness not related to the study (broken wrist, erysipelas and flu) and 1 because of a change in his chronic pain treatment. Patient age, gender, height, weight, Mg extra and intracellular concentrations (0.91±0.1 and 2.00±0.2 mmol/L respectively), number of treatments (including analgesics) were, at randomization, not significantly different between the two groups (table 1). 15 patients had post herpetic neuralgia, 30 post-traumatic or postsurgical with neuropathic pain for 6±2 years.

Table 1. Demographic data (no significant difference between both groups, data expressed as mean (SD; [min-max]).

<table>
<thead>
<tr>
<th></th>
<th>Magnesium</th>
<th>Placebo</th>
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<tr>
<td>N patients</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 (13; [29-79])</td>
<td>59 (11; [42-78])</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 (7; [157-183])</td>
<td>168 (10; [150-186])</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 (11; [52-87])</td>
<td>77 (20; [40-115])</td>
</tr>
<tr>
<td>Number of treatements</td>
<td>4 (2; [1-6])</td>
<td>4 (2; [1-7])</td>
</tr>
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</table>
Pain scores

Total NPSI score and NS were not significantly different between groups at randomization (table 2). Total NPSI score was not different at D29 between placebo and magnesium (p=0.8569). A temporal difference between D0 and D29 was, however, significant for Mg (19 vs 15, p=0.0011) as well as for the placebo group (19 vs 16, p=0.0065). Significant differences existed for Mg, concerning the subgroups Squeezing (0.0088), Paroxystic pain (0.0115), Paraesthesia (0.02) and for Placebo, Squeezing (0.0223).

Mean NS pain, maximal NS pain were not different at D29 between placebo and magnesium (p=0.6295; p=0.7460 respectively). The number of paroxysms was significantly different at D29 (p<0.05). A temporal difference between W-1 and W4 was significant for Mg as well as for the placebo group (table 2), as mean NS and maximal pain both decrease significantly. The number of paroxysms diminished significantly with Mg and increased with placebo.

– HAD: At D0 and at D29, anxiety (A) and depression (D) were not significantly different in placebo and magnesium groups [(D0: 0.7954 (A) and 0.6294 (D) and D29: 0.5803 (A) and 0.3795 (D)].

– SF 36: The score was not significantly changed between placebo and Mg at D0 or D29 for any of the SF36 items. There was, however, a temporal change between W-1 and W4 for both groups concerning the item “physical health” (p<0.05) and for magnesium only concerning “emotion” (p=0.0021).

Discussion

The aim of this double-blind randomised clinical trial was to investigate if oral Mg supplementation in neuropathic patients would help in alleviating pain of neuropathic origin, as had been suggested in preclinical studies [1, 3, 13, 19, 20] and in some clinical studies [24-29]. This study showed that both Mg and placebo groups had improved pain reports, but Mg did not significantly improve the pain indicators when compared to the placebo group. NPSI, which is a questionnaire shown to be responsive to treatment, was not modified by the treatment while mean and maximum pain were improved with the protocol but in a similar way.
fashion in both groups. Pain score improvements were far below those estimated before the study and such an amplitude of the placebo effect was not expected. These results contrast with other clinical studies [30, 32] where the methodology and/or the route of administration were different: Mg was used either IV [30, 32] or orally, but for a longer period [23]. The main observation of the present randomised trial is the placebo effect in the pain report and in the quality of life, with the improvement of the item physical health of the SF36 questionnaire in both groups. Indeed, in the patient–clinician relationship, the clinician’s words can have a powerful effect on the expectations and subsequent neurobiological changes in the patient [37, 38], resulting in enhanced analgesia, although an opposite effect, nocebo hyperalgesia may also occur [39].

It is interesting to note, however, that with time the Mg group presented two significant changes compared to baseline: the diminished number of paroxysms and an improved emotional component in the SF36 questionnaire. Firstly, the number of paroxysms decreased significantly in the Mg group, while it increased in the placebo group. The suddenness and unexpected occurrence of these violent paroxysms of pain make the patients very fragile as regards anticipation of the next bout of coming pain that may occur at any time, often in the middle of the night, breaking the sleep rhythm [40]. Secondly, emotion is improved in the Mg group only: this is interesting as a body of publications stress the involvement of Mg in cognitivo-affective functions. Mg homeostasis is proposed to be involved in biochemical dysregulations contributing to psychiatric disorders [41]. A significant association between Mg imbalance and cognitive impairment has been shown in hospitalized patients [42] and Mg therapy in animals is effective in facilitating cognitive recovery following brain injury in a task and dose-dependent manner [43]. Furthermore, NMDA antagonists modulate the impact on the nucleus accumbens in animals [44], a cerebral region involved in motivation and reward. Mg deficiency leads to enhanced depression-like behavior sensitive to chronic antidepressant treatment and brain magnesium levels are significantly correlated with several anxiety-related behavioral parameters [45]. These results emphasize the hypothesized, and possibly causal, association between magnesium status and emotionality, although HAD did not show any change in our study, probably because our patients were in a normal mental state at randomization. Considering Mg concentrations, no Mg deficiency was detected and the homeostatic mechanism was such that these concentrations were not modified by the Mg treatment; it might be however that the dysfunction of NMDA receptors in this long-standing neuropathic pain is such that the impact of Mg is limited to the reduction of the number of paroxysms and that larger plasmatic levels of magnesium would be required to act significantly on background pain when estimated by NPSI and NS. The concomitant improvement of emotion and frequency of pain paroxysms may be the expression of a similar phenomenon. Indeed, the pain matrix shares common anatomical regions with emotion, with the implication of multi integrative structures [46] like the anterior cingulate cortex, regions involved in pain control such as the periaqueductal grey or basolateral nuclei of the amygdale [47]. It may be hypothesised, but this was not demonstrated in this present study, that the lesser occurrence of paroxysms and hence the diminished anticipation of pain might have improved the emotional component by reducing the stress [48] associated with chronic pain.

Conclusion

This randomised clinical trial could not demonstrate any significant difference in pain scores between oral Mg and placebo in 45 patients suffering from neuropathic pain. A large placebo response was observed with an improvement of all patients in pain report and quality of life. This study contrasts with previous preclinical results but may suggest an influence of Mg on pain paroxysms and affective functions. Frequency of pain paroxysms, emotional impact and their relationship will be studied further, in human and in animals, as they constitute major aspects of pain alleviation in chronic pain conditions.

Disclosure

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None of the authors has any conflict of interest to disclose.
References


