Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial

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Abstract. To evaluate the efficacy and safety of oral magnesium supplementation, with magnesium chloride (MgCl₂), in the treatment of newly diagnosed depression in the elderly with type 2 diabetes and hypomagnesemia. Twenty-three elderly patients with type 2 diabetes and hypomagnesemia were enrolled and randomly allocated to receive either 50 mL of MgCl₂ 5% solution equivalent to 450 mg of elemental magnesium or Imipramine 50 mg daily during 12 weeks. Widowhood or divorce in the last six months, alcoholism, degenerative illnesses of the nervous central system, recent diagnosis of diabetes, previous or current treatment with antidepressants, chronic diarrhea, use of diuretics, and reduced renal function were exclusion criteria. Hypomagnesemia was defined by serum magnesium levels < 1.8 mg/dL and depression by Yasavage and Brink score ≥ 11 points. The primary trial end point was the improvement of depression symptoms. At baseline, there were no differences by age (69 ± 5.9 and 66.4 ± 6.1 years, p = 0.39), duration of diabetes (11.8 ± 7.9 and 8.6 ± 5.7 years, p = 0.33), serum magnesium levels (1.3 ± 0.04 and 1.4 ± 0.04 mg/dL, p = 0.09), and Yasavage and Brink Score (17.9 ± 3.9 and 16.1 ± 4.5 point, p = 0.34) in the groups with MgCl₂ and imipramine, respectively. At end of follow-up, there were no significant differences in the Yasavage and Brink score (11.4 ± 3.8 and 10.9 ± 4.3, p = 0.27) between the groups in study; whereas serum magnesium levels were significantly higher in the group with MgCl₂ (2.1 ± 0.05 mg/dL) than in the subjects with imipramine (1.5 ± 0.07 mg/dL), p < 0.0005. In conclusion, MgCl₂ is as effective in the treatment of depressed elderly type 2 diabetics with hypomagnesemia as imipramine 50 mg daily.

Key words: depression, magnesium, elderly, type 2 diabetes, imipramine

Depression in the elderly is usually persistent and related to medical comorbidity and disability that may be associated with long-term declines in medical and functional status [1, 2]. Furthermore, depression in elderly patients is not only highly prevalent but frequently it is neither recognized nor treated [2], negatively affects the course of diabetes, and is associated with an increased risk of mortality [3].

Recently, based on a meta-analysis that recorded 39 studies having a combined total of 20,218 subjects, Anderson et al. [4] reported that diabetes doubles the odds of depression in the elderly. Because physical and psychosocial changes occur as people enter old age, the elderly are in a developmental phase of life with its own unique challenges that affect the management of both diabetes and depression [5, 6]. In this regard, evidence suggests that depression is related to poorer glycemic control [7] and that depression and diabetes, particularly in older people, have a synergistic interaction that worsens its prognostic [8]. Thus, identifying and
treating depression in the elderly with diabetes is strongly recommended [9].

Total magnesium is significantly lower during depression and increases after recovery, among depressed patients [10]; in addition, the psychiatric symptoms of magnesium deficiency are unspecific, ranging from apathy to psychosis [11]; and more recently, results from an age- and gender-matched case/control study strongly suggests that hypomagnesemia is independently associated with depressive symptoms in the elderly with diabetes [12]. These findings raise the possibility that magnesium deficiency is the cause of major depression and related to mental health problems [13]; however, systematic clinical data about magnesium levels in major depression patients according to psychological profile are not available [14]. Thus, the aim of this study was to evaluate the efficacy and safety of oral magnesium supplementation, with magnesium chloride (MgCl2), in the treatment of newly diagnosed depression in the elderly with type 2 diabetes and hypomagnesemia.

Materials and methods

With the approval of the protocol by the Mexican Social Security Institute Research Committee, and after obtaining the subject’s informed consent, a randomized, active control equivalent trial was carried out. Individuals were recruited from the outpatient Primary Level Medical Care offices in Durango, a city in northern Mexico.

Elderly subjects, aged 60 years or more, were eligible to participate if they had type 2 diabetes hypomagnesemia, and newly diagnosed depression.

Twenty-three eligible subjects were randomly allocated to receive either magnesium supplementation or imipramine for 12-weeks. Because MgCl2 solution shows a higher bioavailability than other commercial magnesium preparations [15], the MgCl2 solution (50 g of MgCl2 per 1 000 mL of solution - 5% solution) was the magnesium supplement used. In fasting conditions, subjects in the MgCl2 group drank 50 mL of the 5% solution daily to receive 2.5 g of MgCl2 equivalent to 450 mg of elemental magnesium. Subjects in group B received 25 mg of imipraminedaily, which was increased according to their response until a maximum of 150 mg per day during 12 weeks. Computer-generated random numbers were used to assign participants to magnesium supplementation or imipramine groups. The final distribution was as follows: 12 subjects with MgCl2 (Group A) and 11 subjects with imipramine (figure 1).

Widowhood or divorce in the last six months, alcoholism, degenerative illnesses of the nervous central system, diagnosis of diabetes ≤ 6 months, chronic diarrhea, use of diuretics, and reduced renal function were exclusion criteria; in addition, because of interactions between magnesium and psychotropic drugs [16], previous or current treatment with antidepressants were also exclusion criteria. Before their inclusion in the study, all the subjects were clinically evaluated and laboratory tested in order to determine the presence of exclusion criteria.

High blood pressure was identified in 10 (83.3%) and 8 (72.7%) of the subjects in the magnesium and imipramine groups, p = 0.64. During the 12 weeks of intervention, to control glycemia, all the patients received standardized doses of glibenclamide (5 mg t.i.d) and a low fat diet based on 21% of daily energy intake from fat, less than 10% of daily energy intake from saturated fat, 21% from protein, and 58% from carbohydrates. Total caloric intake was calculated based on 30 kcal per kg per day ideal body weight [17].

The primary trial end point was the improvement of depression symptoms. Sample sizes were estimated based on a statistical power of 80%, alpha value 0.05, and allowing non-improvement of depression symptoms in 30% of the subjects receiving MgCl2 or imipramine. The required sample size to detect a treatment effect was 11 subjects in each group.

Definitions

Hypomagnesemia was defined by serum magnesium levels < 1.8 mg/dL. Diagnosis of depression was performed using the scale of Yasavage and Brink [18] which recognizes symptoms of depression and is validated for use in the elderly Mexican people. A score of 21 to 30 points is indicative of moderate to severe depression, 11 to 20 points mild depression, and 0 to 10 points absence of depression. The scale has a sensitivity and specificity of 0.91 and 0.72 [19]. Eligible subjects for this study were required to have a Yasavage and Brink score equal or greater than 11 points.

Measurements

At baseline and the end of the study, the Yasavage and Brink scale was applied, and fasting glucose levels, glycosylated hemoglobin (HbA1c), and lipid profile were measured. In addition, serum magne-
Serum magnesium was measured by colorimetric method, with intra- and inter-assay variations of 1.0 and 2.5%, respectively.

Serum glucose was measured by the glucose-oxidase method; its intra- and inter-assay variations were 1.5% and 2.1%. The lipid profile was measured by enzymatic methods; the intra- and inter-assay variations were 2% and 3.0%.

All measurements were performed in a Data pro Plus clinical auto-analyzer (Arlington TX, USA).

**Statistical analysis**

The pre-planned intention-to-treat analysis of the primary study end-point, the improvement of depression symptoms, were carried out for all the randomly allocated participants who satisfactorily completed the follow-up. To establish the differences between the groups we used Mann-Whitney U test and Fisher’s Exact test. A p value < 0.05 defined the level of statistical significance. The data were analyzed using the SPSS 12.0 statistical package (SPSS Inc., Illinois USA, 1998).

**Results**

A total of 265 elderly with type 2 diabetes were screened. Prevalence of depression, hypomagnesia levels were measured every 4 weeks. The person assessing outcomes was blinded to the group assignment.

Anthropometric measurements were assessed using conventional protocols. Height and weight were taken with the subjects in light clothing and without shoes. The body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared). Waist circumference was taken as the minimum circumference at umbilicus level.

Adherence to pharmacological treatment was assessed every month by personal interview, and tablet count.

**Figure 1.** Study participant flow diagram.
mia, and depression plus hypomagnesemia was 44.9, 38.9, and 13.2%, respectively.

Thirty-five subjects fulfilled the inclusion criteria. Of these, 8 refused to participate and 23, 12 women and 11 men, were enrolled and randomly allocated, 12 in the group of MgCl2 and 11 in the group of imipramine. Overall, the average Yasavage and Brink score and serum magnesium levels were 17.0 ± 4.7 and 1.3 ± 0.3 mg/dL, respectively. A total of 16 (69.6%) individuals had light and 7 (30.4%) moderate to severe depression.

The average dose of imipramine required to achieve a beneficial effect on depressive symptoms was 50 mg daily. All the subjects in the imipramine group had at least one drug-related adverse event such as dry mouth, constipation, sweating, hot flashes, disorders of visual accommodation and blurred vision, urination disorders, fatigue, somnolence, increased anxiety, sleep disorders, confusion, disorientation and auditory hallucinations, fine tremor, headaches and dizziness, sinus tachycardia, nausea, anorexia, and itch. Two (18.2%) individuals dropped out by the side effects of imipramine. On the other hand, mild abdominal pain and diarrhea were present in 3 (25%) individuals who received MgCl2; there were no dropped-outs due to MgCl2. Adherence was achieved by 91.7% and 72.7% of the subjects in the MgCl2 and imipramine groups, respectively.

The preplanned intention-to-treat analysis of the primary study end-point was performed in the 21 participants who completed the follow-up. There were no differences by age (69 ± 5.9 and 66.4 ± 6.1 years, p = 0.39) and duration of diabetes (11.8 ± 7.9 and 8.6 ± 5.7 years, p = 0.33), in the groups with MgCl2 and imipramine, respectively. The distribution of light (66.7 and 66.7%) and moderate to severe depression (33.3 and 33.3%) was similar in the groups of MgCl2 and imipramine.

Table 1 shows the clinical characteristics of the participants at baseline and at the end of follow-up. At baseline, serum magnesium and Yasavage and Brink scores were similar in both groups; at the end, subjects who received magnesium supplementation significantly increased their serum magnesium levels. The Yasavage and Brink score significantly decreased in both groups; at the end of follow-up there were no significant differences between the groups.

A total of 7 (58.3%) and 9 (81.2%) patients in the groups of MgCl2 and imipramine significantly improved their symptoms of depression, p = 0.37.

**Discussion**

Our results show that oral magnesium supplementation with MgCl2 is as effective in the management of depressed elderly type 2 diabetics with hypomagnesemia as imipramine 50 mg daily. In addition, our results also show the safety of MgCl2 in the treatment of the elderly and that it is better tolerated than imipramine. These findings support the statement that serum magnesium should be determined when there are symptoms of depression, particularly in the elderly with diabetes.

Major depression is a mood disorder that can adversely affect a person’s life and sometimes to such an extent that suicide is attempted. Therefore,

**Table 1. Basal and end characteristics of elderly with type 2 diabetes who received magnesium chloride (MgCl2) or imipramine.**

<table>
<thead>
<tr>
<th>N</th>
<th>Baseline MgCl2 (12)</th>
<th>Baseline Imipramine (9)</th>
<th>End MgCl2 (12)</th>
<th>End Imipramine (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yasavage and Brink score</td>
<td>17.9 ± 3.9</td>
<td>16.1 ± 4.5</td>
<td>11.4 ± 3.8 &lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.9 ± 4.3 &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>194.3 ± 59.0</td>
<td>183.4 ± 68.0</td>
<td>191.1 ± 59.7</td>
<td>183.1 ± 74.3</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.9 ± 1.6</td>
<td>9.0 ± 1.7</td>
<td>8.8 ± 1.2</td>
<td>8.9 ± 1.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134.1 ± 19.2</td>
<td>141.0 ± 20.1</td>
<td>135.2 ± 20.5</td>
<td>143.7 ± 19.9</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.2 ± 3.9</td>
<td>84.7 ± 6.1</td>
<td>77.0 ± 3.6</td>
<td>87.6 ± 6.4</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.0 ± 0.4</td>
<td>1.0 ± 0.3</td>
<td>0.9 ± 0.4</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>169 ± 53.8</td>
<td>148.0 ± 77.3</td>
<td>122 ± 52.6 &lt;sup&gt;a&lt;/sup&gt;</td>
<td>142.7 ± 51.9</td>
</tr>
<tr>
<td>HDL-Cholesterol, mg/dL</td>
<td>45.6 ± 20.6</td>
<td>41.0 ± 12.5</td>
<td>49.2 ± 15.4 &lt;sup&gt;a&lt;/sup&gt;</td>
<td>44.6 ± 10.8</td>
</tr>
<tr>
<td>Serum magnesium, mg/dL</td>
<td>1.3 ± 0.04</td>
<td>1.4 ± 0.04</td>
<td>2.1 ± 0.08 &lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5 ± 0.07 &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> p < 0.005 between baseline and end conditions for the subjects in the same group.
<sup>b</sup> p < 0.0005 between magnesium chloride and imipramine groups.
recognizing and treating depression is an important issue in the management of the elderly (5). However, antidepressant drugs are not always effective and have been associated with severe side effects and adverse events [20, 21].

Because magnesium ions regulate calcium ion flow in neuronal calcium channels, helping to regulate neuronal nitric oxide production and neurotransmission, magnesium deficiency has been related to the pathogenesis of neuropaathologies such as depression [13, 22]. Based on case histories showing a rapid recovery (less than 7 days) from major depression using 125-300 mg of magnesium (as glycinate and taurinate) with each meal and at bedtime, recently Eby et al. [13] hypothesized that magnesium treatment could be effective in treating major depression resulting from intraneuronal magnesium deficits. However, to the best of our knowledge, this is the first randomized clinical trial that presents evidence on the efficacy and safety of MgCl2 in the treatment of depression.

In addition, it has been reported in animal models, that increasing the intracellular magnesium concentration, stimulation of sodium/magnesium antiports at a physiological intracellular magnesium concentration, result in an inhibition of sodium/magnesium antiports, improving the effect of imipramine on depression symptoms [23].

During this study, to control hyperglycemia, all the patients received the maximum doses of glibenclamide and a low fat diet; however, antidiabetic treatment, that was individually evaluated and adjusted at end of intervention, was clearly insufficient for achieving adequate glycemic levels. This finding suggests that the improvement of depression in the elderly with type 2 diabetes, seems to be independent of their glycemic status.

Some potential limitations of this study deserve to be mentioned. First, the study was designed as an active control trial. In this regard, a placebo should be administered, whenever possible, to participants in control groups for assessing the efficacy of new treatments in those clinical conditions for which no effective treatment exists [24]. Because imipramine is an effective treatment for depression [25] we compared two active treatment groups without placebo, which is an acceptable way for evaluating the efficacy and safety of a therapy, without ethical implications [26-28], and obtaining reliable information about the new therapy [28]. In addition, the less the study-to-study variability in outcomes, and the few instances of unexplained failure of the control agent are also persuasive reasons for using the active-control trial design [24]. Second, we measured the magnesium confined to serum which is a relatively minor compartment of total body magnesium. However, taking into account that serum magnesium levels shows a high correlation with intracellular free magnesium concentration [25, 26], and both the clearly conveyed aim and primary trial end point of this study, this limitation did not influence our conclusions. Third, the small sample size could be related to the possibility of a type II error in the analysis of data; however, the sample size had the power to show significant differences intra- and inter-groups when baseline and end conditions were compared, thus, the possibility of type II error is minimal.

Conclusion

Our results show for the first time the efficacy and safety of MgCl2 for the treatment of depression in the elderly with type 2 diabetes and hypomagnesemia, supporting the statement that serum magnesium should be determined when there are symptoms of depression, particularly in the elderly with type 2 diabetes.

Acknowledgments

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