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The Effect of Magnesium Oxide on Hyperphosphatemia in Female Hemodialysis Patients

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Background: Hyperphosphatemia is a common problem in hemodialysis patients for which various binders are used to control this problem.
Objectives: This study aims to assess the effect of magnesium oxide on controlling serum phosphorus levels and evaluate its side effects.
Patients and Methods: We studied 39 hemodialysis patients with hyperphosphatemia. Patients were randomly divided into two groups, trial and control. The trial group received magnesium oxide. Its dose was titrated according to weekly magnesium levels that were checked for 4 weeks. Phosphorous was also checked weekly in both groups. Data were analyzed by SPSS 15 software. P-values less than 0.05 were considered significant.
Results: A total of 27 males and 12 females with a mean age 54.01±17.20 years were divided into the trial (21 patients) and control (18 patients) groups. Serum phosphorous levels did not significantly decrease (P = 0.994). However the mean phosphorous level in females showed significant correlation with time, as a significant quadratic trend throughout time was observed (P = 0.001). A significant ascending trend in mean magnesium levels was observed in the trial group compared to the control group at the end of the study (P < 0.001).
Conclusions: Although magnesium oxide was well tolerated by the study patients and lacked serious complications, it could not decrease phosphorous levels. In order to better assess these results we recommend that larger, multicenter studies with longer follow up that uses other magnesium compounds be designed.

Keywords: Hemodialysis; Hyperphosphatemia; Phosphorus; Magnesium Oxide

1. Background

The number of dialysis patients is rapidly increasing in our society. Among these patients, a variety of problems exist, such as high serum phosphorus (P) levels. Hyperphosphatemia, a frequent occurrence in dialysis patients is associated with bone disease, pruritus, progressive renal failure, increased cardiovascular events, and left ventricular hypertrophy (1-3). Phosphorous binders currently used for this condition are either expensive or toxic (3). In this regard magnesium (Mg) binders are available and inexpensive. The affinity of Mg for P is less than aluminum or calcium (Ca) however the lower intestinal absorption of Mg leaves a greater amount of Mg available for binding with P within the gut lumen over time (4). There are few studies that have used Mg as a P binder (5, 6). We were unable to locate any study that had used Mg oxide for control of hyperphosphatemia. However, one study reported lower bioavailability of Mg oxide with significantly higher, equal absorption and bioavailability of Mg chloride and Mg lactate (7). According to the limited studies performed, Mg provided similar serum P control compared to standard treatments. In addition, Mg was safe and well tolerated. Its therapeutic use has other benefits in addition to P binding, such as decreasing the risk of arterial calcification, cardiovascular death and prevention of bone loss (1-6).

2. Objectives

The current study assessed Mg oxide for the control of hyperphosphatemia in hemodialysis (HD) patients.

Implication for health policy/practice/research/medical education:
Magnesium oxide well tolerated by the hemodialysis patients but it could not decrease phosphorous levels. Due to complex relationship between Ca, Mg, P, PTH and vitamin D levels, a larger study with longer duration is necessary.

3. Patients and Methods

Between February and September 2012, we prospectively studied 39 HD patients who underwent dialysis at Sadra Dialysis Center, Shiraz, Iran. Patients were enrolled if they met the following inclusion criteria: HD with duration of greater than three months, 3 times per week, serum P level > 5.5 mg/dL despite dietary P restriction and serum Ca > 8 mg/dL. Exclusion criteria were Mg level > 3 mg/dL, recent acute illness with a change in appetite or diet, and recent change in CaCO3 or Calcitriol dosage, or start of a P binder agent. Of 180 patients assessed for eligibility, 42 patients met the inclusion criteria for study entry. We randomly assigned patients into the trial (n = 24) and control (n = 18) groups based on a randomization table. In the trial group, 3 patients developed abdominal cramps during the study and were withdrawn; therefore we studied 39 HD patients.

3.1. Study Protocol

The study protocol of this prospective randomized clinical trial complied with the Declaration of Helsinki and was approved by the Ethics Committee of Shiraz University of Medical Sciences. All patients who participated provided written informed consent. Patients in the trial group received Mg oxide (Mg®, 21st Century®) at a dose of 250 mg orally for 4 weeks. The drug dose was titrated according to the weekly serum Mg levels. Patients in both groups were on either CaCO3 or Calcitriol according to their previous P and parathyroid hormone (PTH) lab data. Mg^{2+} (1 meq/L) and Ca^{2+} (2.5 meq/L) of dialysate fluid remained intact during the trial. The trial group was observed closely for any side effects of Mg oxide. Blood samples were taken by trained nurses at the start and end of the trial to check levels of PTH, Ca, Mg, P, and albumin (Alb). For weekly levels of Mg and P, we obtained samples prior to the onset of the HD session. The samples were centrifuged at rate of 3000 /minute for 10 minutes after which they were frozen at -20°C. We used the colorimetry method for Ca, Mg, P and Alb measurements. PTH was measured by immunoradiometric assay (IRMA).

3.2. Statistical Analysis

Data were analyzed by SPSS 15 software. Chi-square, Pearson correlation coefficient, and independent t-tests were used for comparison of appropriate variables. Pre-trial, during, and post-trial data were analyzed by the paired t-test, ANOVA, and repeated measurement tests. We used the Kolmogorov-Smirnov Z test to determine that the distribution was normal in the groups (P > 0.05). A P value of < 0.05 was considered significant.

4. Results

There were 27 male (69.20%) and 12 female (30.80%) patients with a mean age of 54.01 ± 17.20 years (range: 20-83 years) who were randomly divided into the trial (n = 21) and control (n = 18) groups. Of underlying diseases, 43.62% (17) patients had diabetes mellitus (DM) and 30.80% (12) patients had hypertension (HTN). The mean time patients were on HD was 2.47 ± 0.91 years (trial) and 3.00 ± 1.41 years (control). As shown in (Table 1), there was no significant difference between the two groups in terms of baseline data. We found a significant, direct correlation between baseline PTH and baseline Mg levels (r = 0.33, P = 0.038). The daily mean consumption of Mg oxide for the trial group during the study was 1.57 ± 0.48 tablets which was equivalent to 392.50 ± 120.00 mg. The weekly mean consumption of Mg oxide was 11.11 ± 3.48 tablets which was equivalent to 2.77 ± 0.87 g.

Table 1. Comparison of Baseline Characteristics of the Studied Groups [a, b, c]

Baseline Variables	Trial (n = 21)	Control (n = 18)
Age, y	56.28 ± 15.60	52.05 ± 18.83
Sex		
Male	14 (66.67)	13 (72.22)
Female	7 (33.33)	5 (27.78)
HD per week	-	-
Two times	9 (42.86)	6 (75.00)
Three times	12 (57.14)	12 (25.00)
Time on HD, y	1.00 ± 0.74	1.02 ± 0.54
Underlying diseases		
DM	11 (52.38)	6 (33.33)
HTN	6 (28.57)	6 (33.33)
Other	4 (19.05)	6 (33.33)
Rocatrol use		
No	15 (71.42)	7 (3.89)
Yes	6 (28.57)	11 (96.11)
$CaCO_3$ use		
No	8 (38.09)	4 (22.22)
Yes	13 (61.90)	14 (77.78)
Calcitriol use, %		
No	15	7
Yes	6	11
Kt/V, Dialysis adequacy	2.47 ± 0.091	3.00 ± 1.41
Cr, mg/dL	6.68 ± 1.41	7.01 ± 1.91
BUN, mg/dL	45.81 ± 8.63	53.37 ± 14.85

[a] Abbreviations: BUN, blood urea nitrogen; $CaCO_3$, calcium carbonate; Cr, creatinine; HD, hemodialysis.
[b] Data are presented as Mean ± SD or No. (%).
[c] There is no significant difference between two groups in baseline data (P < 0.05).

4.1. Effect of Magnesium Oxide on Phosphorous and Magnesium

The mean profiles for P were similar between the trial and control groups, which remained similar over time (Figure 1). Hence, the mean for P did not significantly decrease in the trial group compared to the control group

(P = 0.667). No linear correlation existed between mean Mg and P levels throughout the study in the trial group (P = 0.091). According to the repeated measures, no significant difference existed in the overall mean for P value during the study period between both groups (P = 0.639). The mean P level was not constant throughout the study period in female studied group; as there was a significant U shape correlation or quadratic trend throughout time (P = 0.001). The mean profiles for Mg levels between both groups were not similar (Figure 2). There was a significant interaction effect between the two groups (P = 0.001). Despite higher baseline Mg level in the control group compared to the trial group (P = 0.010), we observed a higher non-significant rise in Mg level in the trial group compared to the control group during the first, second and third weeks of the trial (Table 2). During the fourth week trial this ascending trend became significant (P = 0.001), whereas the control group had a descending trend after the second week of the trial in mean Mg levels (Figure 2).

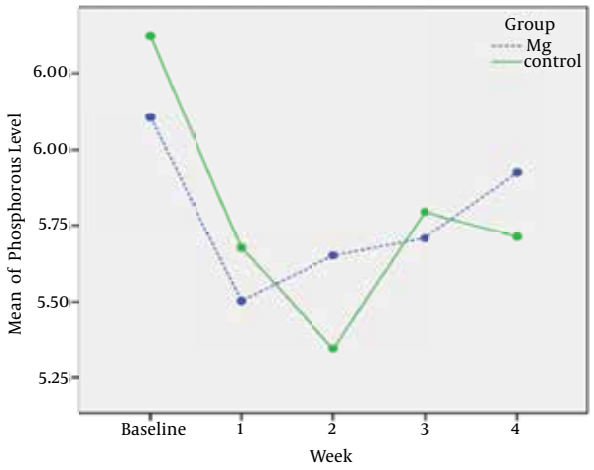

Figure 1. Comparison of the Mean Phosphorous Levels Between Groups

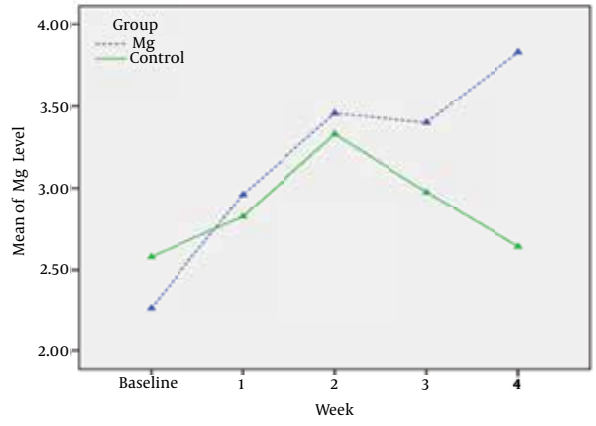

Figure 2. Comparison of the Mean Magnesium Level Between Groups

Table 2. Comparison of the Biochemical Data Between Hemodialysis Groups [a]

Variables	Trial (n = 21)	Control (n = 18)
P, mg/dL [b]		
Baseline	6.10 ± 0.45	6.37 ± 0.49
After 1 week	5.50 ± 0.87	6.67 ± 0.93
After 2 weeks	5.65 ± 0.76	5.34 ± 0.68
After 3 weeks	5.70 ± 1.30	5.79 ± 0.67
After 4 weeks	6.92 ± 0.73	6.71 ± 1.18
Mg, mg/dL [c]		
Baseline	2.26 ± 0.33	2.59 ± 0.41
After 1 week	2.95 ± 0.45	2. 91 ± 0.44
After 2 weeks	3.45 ± 0.70	3.24 ± 0.75
After 3 weeks	3.40 ± 0.87	2.97 ± 0.48
After 4 weeks	3.83 ± 0.79	2.64 ± 0.36
Alb, g/dL		
Baseline	3.41 ± 0.23	3.81 ± 0.55
After trial	3.52 ± 0.46	3.57 ± 0.33
P value	0.294	0.145
Ca, mg/dL		
Baseline	8.70 ± 0.44	8.87 ± 0.57
After trial	8.49 ± 0.57	8.73 ± 0.82
P value	0.058	0.318
PTH, mg/dL		
Baseline	390.97 ± 327.74	417.25 ± 265.88
After trial	414.52 ± 387.37	323.88 ± 277.02
P value	0.059	0.120

[a] Abbreviations: Alb, albumin; Ca, calcium; Mg, magnesium; P, phosphorus; PTH, parathyroid hormone.
[b] According to the repeated measures, no significant difference existed in the overall mean for P between both groups (P = 0.639).
[c] There was a significant difference between trial and control groups when comparing the after 4 weeks values (P < 0.001).

4.2. Effect of Magnesium Oxide on Calcium, Albumin and Parathyroid hormone Levels

We compared the means for Ca, PTH, Mg, and Alb between the groups by adjusting for the corresponding baseline values. There was no significant effect of Mg oxide on the mean Ca (P = 0.666) and Alb (P = 0.869) levels. There was a significant difference in the end of trial PTH levels between both groups (P = 0.017).

5. Discussion

Hyperphosphatemia, a frequent occurrence in HD patients, is one of the most important factors in uremic progression (8), for which control of serum P level leads to improved survival (9). Management of hyperphosphatemia in HD patients is difficult due to dietary restrictions that lead to inadequate protein intake and malnutrition

(8), impossible nocturnal daily HD, increased the duration and frequency of HD treatment which is not feasible due to high patient numbers, and the rapidly increasing numbers of patients who need HD. The most commonly used treatment modality is P binders which are associated with significant reductions in mortality (10). However, there is a lack of prospective, data that show clear-cut superiority of the available treatment options (9). Mg P binders are more cost effective for the treatment of hyperphosphatemia (11, 12). In the current study, for the first time, we have used Mg oxide as a phosphate binder. Our results were similar to others who used different Mg compounds and showed no significant decrease in P levels in the trial groups (11, 13-15). However in contrast to our findings, one study showed a significant effect of $MgCo_3$/Ca acetate in the reduction of serum P (16). The reason why P in the current study's trial and control groups were almost the same might be due to the fact that our patients did not obey dietary restrictions. We were unable to insist on tight restrictions since many of these patients already had malnutrition due to less protein-calorie.

We observed no serious adverse effects, which were similar to a study by de Francisco et al. (14). The concentrations of Mg and Ca in the dialysate bath were intact. In studies by O'Donovan et al. and Parsons et al. the dialysate solutions did not contain Mg (15, 17). Although we did not make any changes in the dialysate Mg concentration, we closely monitored serum Mg levels and prevented the occurrence of life-threatening hypermagnesemia. Clinical symptoms and ECG abnormalities of hypermagnesemia appear only when the level of serum Mg exceeds 4 mg/dL (18). In our study the serum Mg level significantly increased during the study in the trial group which contrasted the study by Tzanakis et al. who reported that serum Mg levels were lower in the trial group compared to the control group (11). It has been mentioned in some studies that Mg salts are not particularly effective as P binders and large doses are required for control of P, which leads to adverse gastrointestinal effects for which adjustment of dialysate Mg is necessary (19-22). PTH was significantly higher in the trial group compared with control group which remained significantly high in the trial group until the end of the study. A similar study reported no significant difference in serum PTH levels between the studied groups (11). The suppressive effect of Mg on PTH might have been observed if our study had continued for a longer period. Limitations of the present study included small sample size, single center study, short follow up period, and lack of evaluation of the impact of Mg supplement on patients' bone turnover and cardiovascular system. In order to achieve acceptable serum P levels, combination therapy is required in a remarkable percentage of HD patients. For this purpose, Mg supplements seem to be safe and cost effective. Because of the complex relationship between Ca, Mg, P, PTH and vitamin D levels, a number of larger studies with longer duration and similar characteristics are necessary to correctly judge the changes in each of these parameters.

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Authors' Contribution

Maryam Pakfetrat and Shokouh Sharifpour designed and performed experiments; Leila Malekmakan analyzed data; Jamshid Roozbeh supervised the project; Amir Aslani and Shahrokh Ezzatzadegan Jahromi wrote the main paper; All authors discussed the results, revised and finalized the final draft of manuscript.

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