Renal Replacement Therapy

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Effects of low-dose magnesium oxide on elevated serum magnesium levels and improved constipation in hemodialysis patients: a single-center retrospective study

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Abstract

Background The prevention of hypomagnesemia is critical for improving the life expectancy of patients undergoing hemodialysis (HD). The administration of magnesium oxide (MgO) increases serum Mg concentrations; however, dose adjustments must be done carefully owing to the risk of hypermagnesemia in patients undergoing HD. Additionally, the laxative effects of low-dose MgO on constipation in these patients has not been reported. Therefore, in the present study, we investigated the effects of treatment with low-dose MgO on serum Mg concentration changes and the improvement of defecation in patients undergoing HD.

Methods The present study was a single-center retrospective observational study of 43 patients undergoing maintenance HD at Shirasagi Hospital. The patients' clinical characteristics, including serum Mg concentration, were obtained from the hospital's electronic medical records. In the group who received MgO for constipation, the effectiveness of MgO as a laxative was categorized as effective, ineffective, or unknown on the basis of electronic medical records related to defecation.

Results Of the 43 patients included in the present study, 23 were prescribed supplemental Mg to prevent hypomagnesemia or maintain mild hypermagnesemia and 19 to prevent constipation. All patients received diasylate with an Mg concentration of 1.0 mEq/L. Additionally, 37 patients (86%) were treated with 330 mg/day MgO. The serum Mg concentrations before and 1, 2, and 3 months after the start of MgO were 2.3 ± 0.2, 2.8 ± 0.4, 2.8 ± 0.5, and 2.8 ± 0.4 mg/dL, respectively ($P < 0.001$). Multiple linear regression analysis showed that dry weight was independently associated with changes in serum Mg concentration from before to 1 month after MgO administration (regression coefficient = −0.027; $P = 0.020$). Of the 19 patients evaluated for constipation, 8 (42%) had documented effective bowel movements after the initiation of MgO, 6 had no effect, and 5 were unknown; however, 1 patient in the ineffective group and 2 in the effective group used other laxatives prior to starting MgO.

Conclusions The results of the present study suggest that the administration of low-dose MgO to patients undergoing HD provides a means of increasing serum Mg concentration without causing dangerous hypermagnesemia, that serum Mg concentrations increase relatively easily in lower-weight patients. In addition, this study shows that low-dose MgO may be effective as an initial treatment for constipation in this patient group in a cautious

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manner, but this study did not provide sufficient data for the usefulness of low-dose MgO for constipation in patients undergoing HD.

Keywords Hemodialysis, Magnesium oxide, Hypermagnesemia, Constipation

Background

Patients undergoing maintenance hemodialysis (HD) are at a higher risk of dying from cardiovascular disease [1]. Recently, several studies identified hypomagnesemia as a factor associated with mortality in these patients [2, 3]. Additionally, mild hypermagnesemia is associated with a lower risk of hip fracture [4] while buffering the increased risk of cardiovascular mortality owing to hyperphosphatemia [5] in patients undergoing HD. Therefore, the prevention of hypomagnesemia in patients undergoing HD is critical to improving poor prognosis.

The oral administration of magnesium (Mg) is a simple and effective approach to increase serum Mg concentrations. In fact, Bressendorff et al. [6] reported that oral Mg supplementation improved T_{50}, the time point at which calcium-protein particles are converted from primary to secondary, in patients with stage 3 and 4 chronic kidney disease (CKD). Some studies, however, have reported that oral Mg supplementation in nondialyzed patients with CKD reduced the risk of coronary artery calcification [7], while others have reported that it did not change the risk [8]; therefore, a consensus has yet been reached. On the other hand, multiple studies have shown that a low T_{50} is associated with poor prognosis in patients undergoing HD [9, 10]. As a whole, patients undergoing HD are at an extremely high risk for developing hypermagnesemia after the administration of Mg as a result of their significantly impaired renal function. Therefore, to avoid hypomagnesemia, it is important to determine the safe dosages of magnesium oxide (MgO) in patients undergoing HD.

Patients undergoing dialysis often experience chronic constipation, which has recently been shown to be associated with low mortality [11, 12] and peritoneal dialysis-related peritonitis [13]. The improvement of chronic constipation in these patients is, therefore, important from the perspective of improving poor prognoses. MgO is a safe and effective salt laxative used in patients with normal renal function; however, its effect is dose-dependent because MgO is converted to the osmotic substances magnesium chloride ($MgCl_2$) and magnesium bicarbonate ($Mg(HCO_3)_2$), which increase defecation. In contrast, Mg is primarily excreted by the kidneys and, therefore, cannot be administered at normal doses to patients with impaired renal function, including those undergoing dialysis, owing to the increased risk of hypermagnesemia [14, 15]. There are no reports, however, on the effectiveness of low-dose MgO supplementation, which can be safely used in patients undergoing dialysis, in treating constipation.

The present retrospective study, therefore, aimed to determine the effects of low-dose MgO on both serum Mg concentrations and constipation in patients undergoing HD.

Methods

Patients and study design

The present study was a single-center, retrospective, observational study, which included patients undergoing maintenance HD at Shirasagi Hospital (Osaka, Japan) who were prescribed MgO for at least 3 months between January 2017 and May 2023. Patients with no serum Mg concentration data prior to the start of MgO therapy, as well as those who started MgO < 2 months after the initiation of HD, were excluded.

Data collection

Demographic and clinical characteristics, including age, sex, cause of end-stage kidney disease, duration of dialysis, dry weight (DW), dialysis method, standardized dialysis volume (Kt/V), normalized protein catabolic ratio (nPCR), purpose of MgO prescription, laboratory data, and concomitant drugs were obtained from the electronic medical records maintained by Shirasagi Hospital. Serum Mg concentrations were measured prior to the start of MgO administration and every month for 3 months thereafter. In the group prescribed MgO for constipation, the effectiveness of MgO as a laxative was categorized as effective, ineffective, or unknown on the basis of electronic medical records related to defecation.

Ethical considerations

The protocol for the present study was approved by the Shirasagi Hospital Ethics Committee at Shirasagi Hospital (approval number JCR2023004) and was performed in accordance with the Declaration of Helsinki.

Statistical analyses

Normality of the distribution was examined using the Shapiro–Wilk test, and data with normal distributions are presented as mean ± standard deviation, while those with nonnormal distributions are presented as medians with ranges. One-way analysis of variance (ANOVA) was used to compare serum Mg concentrations before

and after the administration of MgO. The associations between these changes in serum Mg concentrations and patient background factors were evaluated using the Spearman rank correlation test and stepwise multiple linear regression analysis. Data with nonnormal distributions were log-transformed using multiple linear regression analysis. All statistical analyses were performed using EZR, which is a modified version of the R commander equipped with statistical functions for medical statistics [16]

Table 1 Patient characteristics

Sex (male/female)	26/17
Age (years)	70 ± 11
Cause of CKD (*n*)	
Type 2 diabetes mellitus	16
Chronic glomerular nephropathy	5
Nephrosclerosis	11
Other	9
Unknown	2
Dialysis duration (years)	3 [1–26]
Dry weight (kg)	58.6 ± 11.9
Dialysis	
HD/online HDF/intermittent infusion HDF (*n*)	22/20/1
Kt/V	1.55 ± 0.35
nPCR	0.79 ± 0.16
Labs	
Albumin (g/dL)	3.5 ± 0.3
Corrected calcium (mg/dL)	8.9 ± 0.6
Phosphate (mg/dL)	4.7 ± 1.3
Intact PTH (pg/mL)	160 [8–586]
Magnesium (mg/dL)	2.3 ± 0.2
Concomitant drugs (*n*)	
Gastric acid blockers (PPI/H2B)	27 (24/3)
Activated vitamin D (oral/IV pulse)	33 (8/25)
Diuretics	8

CKD, chronic kidney disease; HD, hemodialysis; HDF, hemodiafiltration; *Kt/V*, standardized dialysis volume; nPCR, normalized protein catabolic ratio; PTH, parathyroid hormone; PPI, proton pump inhibitor; H2B, histamine 2 receptor blockade; IV, intravenous

Results

Baseline patient demographics and clinical characteristics

The baseline demographic and clinical characteristics of the 43 patients undergoing HD included in the present study are shown in Table 1.

Of the 43 patients included in the present study, 22 were treated with HD, 20 with online hemodiafiltration (HDF), and 1 with intermittent HDF infusion. The dialysate Mg concentration was 1.0 mEq/L in all patients, and the baseline serum Mg concentration was 2.3 ± 0.2 mg/dL.

Dosage and purpose of MgO

The purpose of the prescriptions and MgO dosages are listed in Table 2.

Of the 43 patients included in the present study, 23 were prescribed Mg supplementation to prevent hypomagnesemia or maintain mild hypermagnesemia and 19 were prescribed Mg supplementation for constipation. The doses were as follows: 37 patients (86%) received 330 mg/day; 3 with 660 mg/day; and 1 with 990 mg/day.

Change in serum Mg level after MgO administration

Figure 1 shows the trend in serum Mg concentrations from before to 3 months after the initiation of MgO treatment, reflecting that serum Mg concentrations increased significantly after the initiation of MgO administration. No cases of symptomatic hypermagnesemia were suspected during the study period, and the two patients (5%) that experienced serum Mg concentrations of 4.0 mg/dL or higher continued on at a reduced MgO dosage.

Correlation between change in serum Mg and patient characteristics

Table 3 shows the results of the investigation of the factors associated with changes in serum Mg concentration after 1 month of MgO administration in 32 patients receiving an MgO dose of 330 mg/day.

DW was negatively correlated with changes in serum Mg concentration ($\rho = -0.360$; $P = 0.043$; Fig. 2). Multiple

Table 2 Dosage and purpose of MgO

	Total (*n* = 43)	Constipation (*n* = 19)	Mg supplementation (*n* = 23)	Other (*n* = 1)
Baseline serum Mg	2.3 [1.8–2.9]	2.3 [1.9–2.9]	2.4 [1.8–2.5]	2.0
Dosage (mg/day)				
250	2	1	1	0
330	37	15	22	0
660	3	2	0	1
990	1	1	0	0

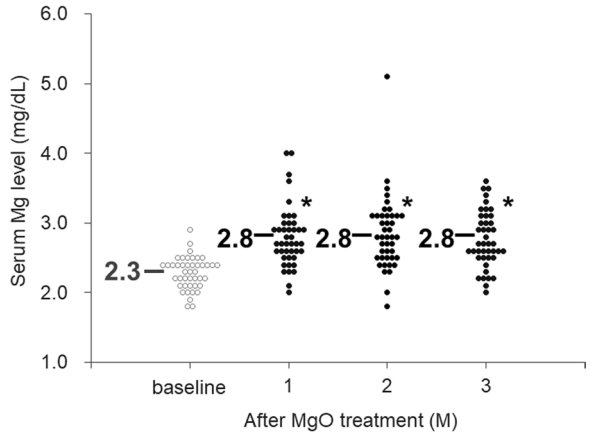

Fig. 1 Change in serum Mg level before and after administration of MgO; open circle: preMgO; closed circle: postMgO

Table 3 Correlation between the serum Mg change and patients' characteristics

	Univariate analysis		Multivariate analysis	
	ρ	*P*-value	Regression coefficient	*P*-value
Sex	–	0.743		
Age (years)	0.040	0.829		
Dry weight (kg)	−0.360	0.043	−0.027	0.020
Kt/V	0.065	0.725		
nPCR	0.061	0.742		
Laboratory data				
Albumin	−0.321	0.073		
Corrected calcium	0.109	0.552		
Phosphate	0.051	0.783		
Intact PTH	0.123	0.503		
Magnesium	0.020	0.912		
Concomitant drug				
Gastric acid blockers	–	0.613		
Activated vitamin D	–	0.902		

Kt/V, standardized dialysis volume; nPCR, normalized protein catabolic ratio; PTH, parathyroid hormone

linear regression analysis showed that DW was associated with variations in serum Mg concentration, independent of serum albumin concentration, baseline serum Mg concentration, and the *Kt/V* ratio (regression coefficient = −0.027; $P=0.020$).

Subgroup analysis of patients prescribed MgO for constipation

The laxative effects of the 19 MgO prescriptions for constipation are shown in Fig. 3. The electronic medical records indicated that 8 of the 19 patients (42%) prescribed MgO for constipation had documented effective bowel movements after the start of MgO, while 6 were ineffective, and 5 were unknown.

Table 4 shows the patient backgrounds of the eight patients in which MgO was effective for constipation and the six cases in which it was ineffective.

Compared with the ineffective group, the effective group received significantly lower doses of MgO ($P=0.035$), while no statistical differences were found in other patient background factors; however, one patient in the ineffective group and two in the effective group used other laxatives prior to starting MgO. None of the patients in the study had undergone gastrectomy.

Discussion

The results of the present study showed that low-dose MgO safely administered to patients undergoing HD increased serum Mg concentrations without causing excessive hypermagnesemia. A meta-analysis of eight studies including 309 patients undergoing HD showed that Mg supplementation resulted in better management of CKD-mineral bone disorder [17]. We believe that the present study is valuable because it provides a methodology for maintaining high serum Mg concentrations in patients undergoing HD. Additionally, the small sample size suggested that low-dose MgO may improve defecation in patients undergoing HD, which may be useful when considering options for treating constipation in patients undergoing HD who are at a high risk of developing chronic constipation.

Most patients in the present study continued an MgO treatment regimen of 330 mg/day, which safely increased their serum Mg concentrations (Fig. 1), and although concentrations exceeding 4.0 mg/dL were observed in a few cases, these were managed with a dose reduction. It may be possible to safely adjust the MgO dosage by monitoring serum Mg concentrations once a month. Additionally, serum Mg concentrations were more likely to be elevated in lower-weight patients (Table 3, Fig. 2), which may be the result of MgO being a fixed-dose oral drug, meaning the dose in terms of body weight is higher in patients with lower body weights. The gastrointestinal absorption of MgO involves the paracellular pathway via tight junctions and the transcellular pathway via the transient receptor potential melastatin (TRPM) 6/7 [18]. TRPM6/7 expression is regulated by Mg intake and intracellular Mg concentrations, and may cause increased Mg absorption during periods of hypomagnesemia [18]. In the present study, the baseline serum Mg concentration was not associated with changes in the serum Mg concentration (Table 3). Because the expression of claudin, a tight junction protein, is decreased in cases of renal dysfunction, resulting in a "leaky gut" [19], Mg absorption

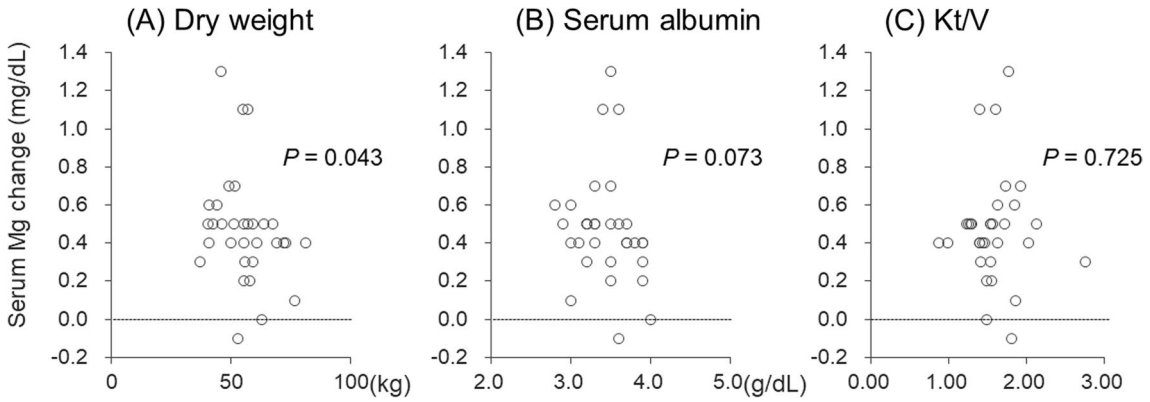

Fig. 2 Correlation between the serum Mg change and patient characteristics. **A** dry weight; **B** serum albumin; **C** standardized dialysis volume

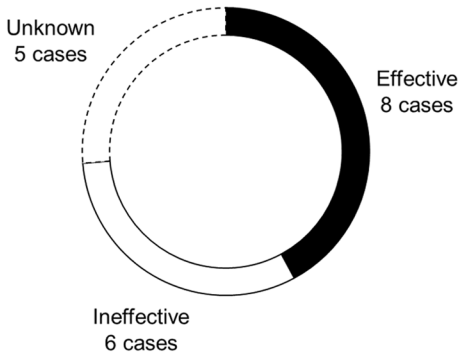

Fig. 3 Laxative effect of MgO for constipation in 19 patients undergoing hemodialysis

Table 4 Subgroup analysis of patients prescribed MgO for constipation

	Laxative effect of MgO		*P*-value
	Ineffective ($n=6$)	Effective ($n=8$)	
MgO dosage	495 [330–990]	330 [250–330]	0.035
Age (years)	66 ± 17	70 ± 10	1.000
Sex (male/female)	5/1	6/2	1.000
Diabetes mellitus	4	4	0.938
Gastric acid blockers	3	5	1.000
Potassium binder	1	0	0.881
Phosphate binder	4	6	1.000
Anticholinergic agent	0	1	1.000
Lubiprostone, linaclotide	1	0	0.881
Elobixibat	0	0	–
Osmotic laxatives	0	0	–
Irritant laxatives	0	2	0.582

via the paracellular pathway appears to be increased in patients undergoing dialysis. Although *Kt*/*V* and serum albumin concentrations are associated with the dialysis removal of free Mg from the serum, they have no apparent effect on changes in serum Mg concentrations, as most of the Mg in the body is distributed throughout the bone and muscle. Therefore, when administering low-dose MgO in patients undergoing HD, although serum Mg concentrations are likely to increase in lower-weight patients, the routine evaluation of serum Mg concentrations may ensure a safe response.

No previous studies, however, have examined the effects of MgO supplementation on constipation in patients undergoing HD. In the subgroup analysis of patients undergoing HD who were prescribed MgO for constipation, approximately half of the patients showed an improvement in defecation (Fig. 3). Previous reports using MgO as a laxative have utilized doses of 1500 mg/day [20–22]; however, a much lower dose was administered to the patients undergoing HD in the present study. In contrast, in the effect of magnesium supplementation on vascular calcification in chronic kidney disease—a randomized clinical trial (MAGiCAL-CKD) study, in which Mg hydroxide was administered at a dosage of 360 mg/day to nondialyzed patients with CKD—soft stool and diarrhea were more frequent in the Mg hydroxide than the placebo group [8]. Those results indicate that even a low dose of MgO may contribute to improved defecation in patients undergoing HD. The lower dose of MgO in the effective group compared with the no-effect group is contrary to theory and the detailed cause is unknown. MgO increments associated with poor efficacy may increase the risk of hypermagnesemia, especially in dialysis patients. Since there was no rational difference in MgO dosage between the effective group and

the noneffective group in this study, if constipation is not improved after low-dose MgO administration, it is advisable to avoid inadvertent increase in MgO dosage and consider adding or changing other laxatives. It has been reported that the MgO dose required to improve constipation was relatively higher in patients with concomitant gastric acid blockers [23]. However, the patient background of this previous report differs from that of the present study in that it included patients after colon surgery and the MgO alone group had a higher average MgO dose of about 1000 mg/day. In this study, it is unclear what factors prevented the concomitant use of gastric acid blockers from affecting the effect of MgO on improving constipation in patients undergoing hemodialysis. Possible factors include lower doses of MgO compared with previous reports and patients with decreased gastric acid secretion owing to complications, such as atrophic gastritis and pancreatitis. There were, however, a few cases of treatment-resistant constipation in the present study, in which patients had already shown a poor response to other laxatives (Table 4). In our previous study on the efficacy of lubiprostone in patients undergoing HD, we found that lubiprostone was effective in 75% of the patients with treatment-resistant constipation who were already using other laxatives [24]. Therefore, low-dose MgO may be one of the initial treatment options administered to patients undergoing HD with the intention of creating a laxative effect; however, it may not have a marked effect on refractory constipation.

The present study had several limitations. First, the small number of patients in the study may have influenced the statistical evaluation, especially in the investigation of factors associated with changes in serum Mg concentrations and the subgroup analysis of the effectiveness of supplemental MgO on improved defecation. Second, as the present study was conducted on outpatients undergoing HD, detailed medication histories could not be confirmed, which may also be a factor related to fluctuations in serum Mg concentrations. In practice, attention should be paid not only to medication noncompliance, but also to hypermagnesemia owing to overmedication with MgO. Third, the effects of improved defecation after the initiation of MgO supplementation were based on the patients' chief complaints, in which there may be bias regarding the method of obtaining the information as well as patient subjectivity. Ideally, changes in bowel movements should be assessed using the Bristol Stool Form Scale (BSFS) and the Constipation Severity Score (CSS); however, these quantitative assessments are difficult to perform in a retrospective study. Since reports of improvements in constipation in patients may indicate satisfaction with defecation or laxatives, and this information is used as a reference in actual clinical practice, we believe that the effectiveness of MgO on improving defecation in patients undergoing HD in the present study cannot be denied. However, for a more quantitative and detailed investigation of the effect of low-dose MgO on improving defecation in hemodialysis patients, it would be desirable to investigate prospectively using a constipation severity scale before and after MgO initiation.

Conclusions

The results of the present study suggest that low-dose MgO administration to patients undergoing HD provides a means of increasing serum Mg concentrations without causing dangerous hypermagnesemia and that it is relatively easy to increase serum Mg concentrations in lower-weight patients. In addition, this study shows that low-dose MgO may be effective as an initial treatment for constipation in this patient group in a cautious manner, but this study did not provide sufficient data for usefulness of low-dose MgO for constipation in patients undergoing HD.

Abbreviations

CKD	Chronic kidney disease
DW	Dry weight
HD	Hemodialysis
HDF	Hemodiafiltration
Kt/V	Standardized dialysis volume
MgO	Magnesium oxide
nPCR	Normalized protein catabolic ratio
TRPM	Transient receptor potential melastatin

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Author contributions

TY performed patient enrollment, sample collection, data interpretation, statistical analyses, and manuscript writing. TF contributed to writing the manuscript. SI, SS, and TY drafted the manuscript. All of the authors have read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author TY on reasonable request.

Declarations

Ethics approval and consent to participate

The present study was approved by the Shirasagi Hospital Ethics Committee (Approval Number JCR2023004) and performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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