



Evaluating intradialytic change of serum magnesium and its relation to intradialytic complications in chronic hemodialysis patients during one-month period

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ABSTRACT

Introduction: The most common important complications of hemodialysis are hypotension, muscle cramps, nausea and vomiting, which play a significant role in the process of dialysis and in the patient's lifestyle.

Objectives: This study aimed to investigate the impact of serum magnesium on incidence of dialysis complications.

Patients and Methods: Two blood samples were obtained from all the patients who were eligible to enter the study for checking their serum magnesium before and after dialysis. Blood pressure was recorded before and after dialysis since the symptoms of cramp, nausea and vomiting were evaluated during dialysis.

Results: Decreased serum magnesium level, throughout dialysis, had a significant direct correlation with intradialytic hypotension (IDH).

Conclusion: Intradialytic hypotension had a direct correlation with the reduction of magnesium level during dialysis.

Implication for health policy/practice/research/medical education:

In a study on a group of hemodialysis patients, reduced serum magnesium level, during and after dialysis, had a significantly direct correlation with IDH.

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Introduction

End-stage renal disease (ESRD) is among the critical life-threatening diseases that render patients in need of receiving a kidney replacement (transplant or dialysis) treatment. However, the limitations in kidney transplants have led several ESRD patients to need dialysis to survive. Hemodialysis is the most prevalent dialysis modality used in many countries and is employed by over 93% of dialysis patients in Iran.

Undergoing dialysis-especially for prolonged periods-inflicts complications and symptoms on patients, the most prevalent and important of which have been examined by many studies.

The most prevalent intradialytic side effects include hypotension (25-50%), muscle cramps (5-20%), nausea and vomiting (5-15%), headache (5%), back pain (2-5%), itching (5%), and fever and chills (below 1%).

Although several studies have been performed on ESRD patients' quality of life, few have exclusively focused on one or several complications and evaluated their association with the change in blood electrolytes during dialysis (1). Among the symptoms which seem to be highly unpleasant and require evaluation for the patients, muscle cramps, nausea, vomiting and hypotension could be mentioned.

Muscle cramps are among the most prevalent complications of hemodialysis. The cramps that are

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typically extremely painful often occur in the final hours of hemodialysis. At this condition, the patients may not experience an appropriate hemodialysis treatment and may lead to early dialysis termination, which could be a reason for hemodialysis inadequacy. Muscle cramps often occur in the lower limbs, but may too involve arms, hands and abdomen.

Several studies have been carried out on the etiology and pathophysiology of this condition and found several factors to be involved in it, including the following parameters: Reduced plasma volume, hypomagnesemia, hyponatremia, tissue hypoxia, carnitine deficiency, increased leptin level

The association between muscle cramps during hemodialysis and changes in blood magnesium levels has recently become a subject of examination. One study reported that a 0.25 mEq/L increase in magnesium level has a significant effect on the reduction of cramps (2).

Objectives

Since creation of the symptoms of cramp, hypotension, nausea and vomiting has an important role in the dialysis process, we aimed to investigate the effects of changes in serum magnesium level during dialysis on the incidence of dialysis complications among hemodialysis patients.

Patients and Methods

Study design

The present study was conducted as a piece of analytical-cross-sectional epidemiologic research. The statistical population included the patients undergoing hemodialysis who were referred to the hemodialysis department at Imam Khomeini hospital of university of medical sciences, Ahvaz, as outpatients and had gone through hemodialysis for at least three months.

All patients underwent three hemodialysis sessions per week, each session lasted four hours. The hemodialysis solution for all patients included 1 mEq/L magnesium, 138 mmol/L sodium, and 2 mEq/L potassium. All patients were dialyzed using a Nipro machine with a polysulfone filter. The dialysis fluid rate was 55 cc/min in all patients and their blood pump flow rate ranged between 300-350 cc/min. The amount of ultrafiltration was set based on each patient's dry weight, and all patients were treated in their dry weight.

Inclusion criteria were as follows: At a minimum of three-month histories of dialysis, no magnesium and carnitine supplement administration, and over 18 years of age.

Patients with the following criteria were excluded from the study: Severe heart disease (EF<35%), active cancer, sepsis, hospitalization over the past weeks, failure to reach the dry weight, calcium and phosphorus level disturbance, history of parathyroidectomy, hypothermia, and active liver problems.

All the patients meeting the inclusion criteria signed written informed consents and underwent two sets of blood sampling, one before and one after hemodialysis, through the arterial line. Blood samples were immediately transferred to the laboratory and stored at -70°C until the start of the analysis. Patients were closely and constantly monitored for complications such as intradialytic muscle cramps, nausea, vomiting, and hypotension, and any complication was recorded in special sheets. The patient's blood pressure was checked before, during (every 30 minutes), and immediately after dialysis using a Richter sphygmomanometer model Exacta 1350. Patients were prohibited from taking antihypertensive drugs before their dialysis sessions. Intradialytic hypotension (IDH) was defined based on the NFK-DOQI guideline (systolic blood pressure drop of over 20 mm Hg or mean arterial pressure drop of over 10 mm Hg after dialysis compared to before dialysis) (3). Ultrafiltration would temporarily stop and 100 cc of 5% hypertonic sodium solution would be injected in case of hypotension.

Blood samples were tested for magnesium, sodium, phosphorus, calcium, liver enzymes, and albumin through immunoturbidimetry and the colorimetric method using a BT3500 autoanalyzer.

Patients' serum magnesium was measured through the colorimetric method using a Selectra analyzer.

Statistical analysis

Results of the tests were recorded in statistical record sheets and underwent statistical analysis in SPSS version 23 statistical software. Logistic regression was conducted to examine the correlation between serum magnesium levels and the variables of muscle cramps, nausea and vomiting, and hypotension, and the odds ratio (OR) value was expressed to determine the correlation. Quantitative values were expressed as mean \pm SD, and the *t* test was conducted to compare them. Accordingly, *t* test and Mann-Whitney U statistical tests were used to compare magnesium serum levels in groups with and without the muscle cramp complication considering a significance level of 0.05.

Results

The present study investigated the changes in magnesium serum levels during hemodialysis and its relationship with the complications occurring during dialysis, especially muscle cramps in hemodialysis patients.

Around 120 patients were initially examined for inclusion criteria, among whom 58 were excluded and the remaining 62 patients entered the study after signing informed consent forms.

After data collection, the research data underwent statistical analysis separately.

In our study, 70% of the patients were male and 30% were female, and their ages ranged between 20 and 75

years (averaged at 54 years). Of 62 patients, 56 patients (90.3%) suffered serum magnesium level drop, 22 (35.5%) had muscle cramps, 10 (16.1%) experience nausea and vomiting, and 35 (56.6%) suffered hypotension during dialysis.

This study showed 100% (35 people) of the patients who suffered hypotension during dialysis had a blood magnesium drop at the same time, while only 77.8% (21 people) of the patients without hypotension during dialysis underwent a magnesium level drop, whereas 22% (6 people) experienced neither hypotension nor intradialytic magnesium level drop.

This study demonstrates the magnesium level changed by 0.5 ± 0.19 mg/L in the group with IDH and 0.22 ± 0.28 in patients who did not suffer IDH.

The mean serum magnesium level before dialysis in the two groups of patients with and without IDH was detected to be 2.37 ± 0.35 mg/dL in patients with IDH and 2 ± 0.3 mg/dL in patients without IDH.

The mean serum magnesium level after dialysis in the patients who suffered IDH was detected a serum magnesium of 1.8 ± 0.04 mg/dL in the patients who suffered from IDH after dialysis and 1.7 ± 0.03 in the patients who did not suffer IDH.

Given the $P < 0.05$, serum magnesium level changes during dialysis had a significant relationship with IDH.

A significant relationship was also observed between serum magnesium levels before dialysis and IDH. Moreover, no significant relationship was observed between serum magnesium levels after dialysis and hypotension before ($P = 0.149$) and during ($P = 0.135$) the hemodialysis.

This study showed that ten patients experienced intradialytic nausea and vomiting, among whom nine

patients (90%) had a dropped serum magnesium concentration while only one patient (10%) did not have a serum magnesium level fall during dialysis.

Furthermore, 52 patients did not experience nausea and vomiting during the study, among whom 47 patients (90.4%) had serum magnesium level drop during dialysis and five patients (9.6%) had no serum magnesium level drop during dialysis.

Our study shows no significant relationship between intradialytic nausea and vomiting and magnesium level drop before, during, or after dialysis (Table 1).

Table 2 indicates the relative frequency and relative frequency percentage of muscle cramps in patients with and without magnesium level drop throughout hemodialysis.

Table 3 indicates no significant relationship between muscle cramps and magnesium level drop before, during, or after dialysis.

Discussion

End-stage renal disease refers to irreversible kidney function loss. The most prevalent intradialytic complications are as follows: hypotension (20-55%), muscle cramps (5-20%), nausea and vomiting (5-15%), and headache (5-25%)

Hemodialysis is the most conventional way to treat ESRD patients worldwide. Despite the rapid advancements in hemodialysis, mortality remains high among hemodialysis patients, and cardiovascular diseases are the main cause of death in these patients (4).

Intradialytic hypotension is among the most prevalent hemodialysis complications and is also associated with cardiovascular diseases (3,5). The prevalence of IDH has increased with the increase in the number of older adults

Table 1. The relationship between changes in serum magnesium level during dialysis, mean serum magnesium level before and after dialysis, and nausea and vomiting

		Number of patients	Mean serum magnesium level	SD	P value
Serum magnesium level before dialysis	Nausea and vomiting	10	2.37	0.47	0.160
	No nausea and vomiting	52	2.18	0.36	0.263
Serum magnesium levels drop during dialysis	Nausea and vomiting	10	0.47	0.39	0.294
	No nausea and vomiting	52	0.36	0.24	0.456
Serum magnesium level after dialysis	Nausea and vomiting	10	1.88	0.31	0.280
	No nausea and vomiting	52	1.79	0.20	0.441

Table 2. Relative frequency and frequency percentage of patients with muscle cramps with and without serum magnesium level drop during dialysis

		Serum magnesium levels drop during dialysis		No Serum magnesium level drop during dialysis		Total
Muscle cramp	No.	20		2		22
	%	90.9		9.1		100
No muscle cramp	No.	36		4		40
	%	90		10		100

Table 3. The relationship between changes in serum magnesium level during dialysis, mean serum magnesium level before and after dialysis, and muscle cramps

		Number of patients	Mean serum magnesium level (mg/dL)	SD	P value
Serum magnesium level before dialysis	Cramp	22	2.23	0.10	0.776
	No cramp	40	2.20	0.37	0.781
Serum magnesium levels drop during dialysis	Cramp	22	0.41	0.31	0.493
	No cramp	40	0.36	0.25	0.524
Serum magnesium level after dialysis	Cramp	22	1.8	0.26	0.894
	No cramp	40	1.81	0.19	0.904

suffering from ESRD and treated with chronic dialysis (6,7). IDH causes hypoperfusion in several organs and can shorten the blood supply of the intestine and increase intestinal permeability. Moreover, IDH can reduce cerebral blood flow and cognitive ability in patients (8). IDH hinders the residual renal function by reducing blood supply to the kidney, which can in turn leave significant impacts on cardiovascular performance, hemoglobin level, and mineral metabolism, increase inflammation and reduce substance clearance of solute with medium to high molecular weight.

Cardiac fibrosis, myocardial ischemia, and arrhythmias can result from hypoperfusion due to IDH (8). The severe reduction in intravascular volume as a result of high ultra-filtration (UF) amount and rate is among the most important driving forces of IDH (5). Fluid therapy and reducing the rate of ultra-filtration during dialysis is a treatment strategy investigated in many clinical trial studies (8). Increasing sodium and calcium concentration in the dialysis fluid can also be another option to treat IDH (3). However, setting a higher sodium level in dialysis fluid can cause a general increase in total body water and eventually increase the need for ultra-filtration. Increasing calcium levels can result in extravascular and intravascular calcification and is thus not a suitable option to treat the hypo-perfusion resulting from IDH.

Increasing the magnesium level in dialysis fluid is another less risky therapeutic option that has been examined in clinical and experimental studies (10). Magnesium is the fourth most important cation in the human body which affects many physiological processes such as cardiac contraction, blood pressure, enzyme stabilization in ATP production reactions, transport through membrane, cell adhesion, and parathyroid function (11). Approximately 99% of the magnesium in the human body is accumulated in bones, tissues, and non-muscle soft tissues.

Multiple studies have indicated the association between low magnesium and ischemic heart disease (IHD), metabolic syndrome, diabetes, atherosclerosis, and vascular diseases (11-13).

The normal magnesium balance is compromised in hemodialysis, and magnesium hemostasis is largely

dependent on its harvest during hemodialysis. The reference for the normal serum magnesium range was 2-2.4 mg/dL in Imam Khomeini hospital laboratory, Ahvaz.

The present study on 62 patients undergoing chronic hemodialysis indicated that the most common intradialytic complications were hypotension, nausea and vomiting, and muscle cramps, respectively. To perform a closer examination of the hypotension, nausea, vomiting, and muscle cramp variables and their relationship with the changes in serum magnesium levels, patients suffering from diabetes, cancer, sepsis, active liver disease, hyponatremia, and Ca and P level disturbances were excluded.

It must be mentioned that some of the aforementioned are considered the reasons for hypotension in hemodialysis patients. Thus, patients who entered the present study did not have any other condition that could be responsible for their hypotension.

It was observed in the present study that all patients suffering from IDH had reduced serum magnesium levels as well. The mean serum magnesium drops after dialysis compared to before dialysis was 0.5 ± 0.22 mg/dL which indicated the magnesium level drop was statistically significant.

On the other hand, patients who did not suffer IDH had a mean serum magnesium level drop of 0.22 ± 0.28 during dialysis which indicated a significant relationship between the lack of IDH and serum magnesium level drop during dialysis. As can be observed, patients who suffered from IDH had a more significant drop in serum magnesium levels compared to those who did not experience IDH.

In terms of the relationship between IDH and serum magnesium level before dialysis, our results indicated that the mean serum magnesium level before dialysis was 2.37 ± 0.35 mg/dL in the group who suffered IDH and 2 ± 0.3 mg/dL in patients who did not experience IDH which suggests a significant relationship between serum magnesium levels before dialysis and IDH. In other words, patients with higher serum magnesium levels before dialysis were more likely to experience hypotension. It is possible that patients with a higher magnesium level at

the beginning of the hemodialysis suffer a greater change in magnesium ions during their dialysis which will show a more significant serum magnesium level drop during dialysis and can explain the more significant drop in blood pressure in this group of patients.

However, the present study found no significant relationship between IDH and serum magnesium levels after dialysis.

Previously, Javaid et al measured serum magnesium levels only once during dialysis and classified patients into three groups of hypomagnesemia, hypermagnesemia, and hypomagnesemia. The study found that hypomagnesemia patients were 3.4 times more likely to suffer IDH (14). However, the results of this study were not consistent with our results in terms of serum magnesium drop during dialysis and its relationship with hypotension (14).

Other similar studies such as the study by Balzer et al on 45 patients have examined the relationship between IDH and dialysis fluid magnesium content. These studies found that the group with a lower dialysis fluid magnesium content was more likely to experience IDH (15,16). Although this study did not examine serum magnesium levels and the relationship between IDH. Hence, their results are indirectly consistent with our findings in terms of the relationship between IDH and intradialytic drop in magnesium level.

This study found that the pre-dialysis magnesium level was higher in IDH patients than in non-IDH patients (2.3 versus 2 mg/dL) and hence this relationship was significant. Although our study did not find a significant relationship between intradialytic serum magnesium drop and magnesium level before and after dialysis and the complication of nausea and vomiting during hemodialysis, however our results were consistent with the aforementioned study in terms of the relationship between pre-dialysis serum magnesium level and IDH complication. The exact reason for this relationship is not fully understood. It is possible that patients with a higher serum magnesium level experience a greater drop in serum magnesium level during hemodialysis which could be directly associated with IDH.

The influence of serum magnesium on cardiovascular function is rather paradoxical. Although increased magnesium level increases stroke volume and contractile strength of the heart by increasing blood flow in coronary arteries, it can cause hypotension as a result of its anti-inflammatory effects in the systemic vascular bed and vascular remodeling improvement (17-19). Regarding muscle cramp complication, the present study found no significant relationship between muscle cramps and changes in serum magnesium levels before, during, and after dialysis.

Naji et al found a similar association between pre-dialysis magnesium levels and intradialytic muscle cramps (9). However, their study did not include the other

parameters examined in our study.

Another study by Lynch et al on 62 ESRD patients treated with chronic hemodialysis indicated that patients would suffer fewer muscle cramps if treated with a dialysis fluid containing more magnesium (2). However, this study did not investigate the changes in serum magnesium level and its association with other intradialytic complications.

Although the exact mechanism of intradialytic muscle cramps is yet to be clarified, low serum magnesium level is among the potential causes of intradialytic cramps. This complication disturbs the function of the sodium/potassium/ATPase pump and the Ca^{2+} /ATPase channel and increases muscle cell irritability (2,20).

Despite the mechanisms mentioned above, results of examining the relationship between magnesium levels and muscle cramps vary widely across different studies.

Our study found no significant relationships between muscle cramp complication and serum magnesium levels before and after dialysis as well as intradialytic changes in serum magnesium levels.

To explain the controversy in results, muscle cramp is a complaint expressed subjectively by the patients and there is no standard tool to examine, confirm, and measure it. Hence, mild cases of muscle cramps may have gone overlooked.

Conclusion

Results of the present study indicated that intradialytic drop in serum magnesium level had a direct and significant relationship with IDH. IDH was revealed to have a significant relationship with pre-dialysis magnesium levels. Patients who experienced IDH had a higher serum magnesium level compared to those who did not suffer IDH. The present study found no significant relationship between post-dialysis serum magnesium level and IDH. Moreover, intradialytic muscle cramps and nausea and vomiting were revealed to have no significant relationship with serum magnesium levels before and after dialysis or intradialytic changes in serum magnesium levels.

Limitations of the study

The study period was short.

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Authors' contribution

Conceptualization: SS.

Methodology: SS and HS.

Validation: SS.

Formal analysis: SA.

Investigation: SS, HS, SA and KAA.

Resources: SS.

Data curation: SA.

Writing—original draft preparation: SS and SA.

Writing—review and editing: HS, SS, SA and KAA.

Visualization: HS and SS.

Supervision: SS.

Project administration: SS.

Funding acquisition: SS.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this paper.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This study was approved by the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical code #IR.AJUMS.REC.1397.856). Accordingly, written informed consent was taken from all the participants before any intervention. This study was extracted from the internal medicine residency thesis by Sanaz Asadi (Thesis #CRD-9703) at this university. Besides, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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