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## The effect of proton-pump inhibitor and ranitidine on the reduction of serum magnesium level and blood pressure in chronic hemodialysis patients with hypotension; a double-blind clinical trial

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### ABSTRACT

**Introduction:** Hypomagnesaemia secondary to the use of proton-pump inhibitor (PPI) is associated with the reduction of blood pressure.

**Objectives:** To determine the effect of PPI and ranitidine on the reduction of serum magnesium level and blood pressure in chronic hemodialysis patients with hypotension.

**Patients and Methods:** In this double-blind randomized clinical trial, 44 hemodialysis patients who met the requirements entered the study. First, blood sample was taken from each of the patients and their serum magnesium level as well as their blood pressure was checked and recorded. Then, the patients in the intervention group received daily doses of ranitidine placebo (150 mg) and pantoprazole (40 mg) and those in the control group received daily doses of pantoprazole placebo (40 mg) and ranitidine (150 mg) for three months. After the intervention, blood samples were taken again in order to assess the patients' serum magnesium level. The obtained data were fed into SPSS Software and analyzed.

**Results:** The mean age of the patients was 60.14±12.98 years. Moreover, 63.6% of the total patients were female. In the group of patients who had received pantoprazole, diastolic pressure reduced significantly at the end of the study as compared to the beginning of the study. Moreover, in the patients receiving pantoprazole indicated a significant reduction of magnesium at the end of the study as compared to the beginning of the study.

**Conclusion:** In this study, a significant relationship was also observed between the use of PPI and hypomagnesemia in hemodialysis patients.

**Trial registration:** The trial protocol was approved in the Iranian Registry of Clinical Trials (identifier: IRCT20150808023559N19; <https://en.irct.ir/trial/42478>, ethical code# IR.ARUMS.REC.1398.295).

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

In patients who receive hemodialysis for a long period, hypotension is associated with higher mortality risks. Therefore, recognizing factors that are involved in the reduction of blood pressure during hemodialysis and removing their effects can be helpful in reducing mortality among hemodialysis patients. In this study, a significant relationship was observed between the use of proton-pump inhibitor and hypomagnesemia in hemodialysis patients.

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### Introduction

Hemodialysis is the most common therapy for end-stage renal disease (ESRD) (1). This complex therapy is

oftentimes accompanied by the absorption of body fluids and water during the ultrafiltration process, which leads to hypotension (2). This condition causes disruptions

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in the excretion of magnesium in patients suffering from advanced chronic kidney disease and ESRD (3). Hemodialysis patients' magnesium balance depends on two main factors; oral absorption/gastrointestinal absorption of magnesium and dialysate magnesium concentration. Recent observations have revealed that hypomagnesemia is associated with lower blood pressure, higher risks of cardiovascular complications, and higher mortality rates among hemodialysis patients (3). There are also reports of hypomagnesaemia developing secondary to all types of proton-pump inhibitors (PPIs). Attacks of hypotension occur in more than half of hemodialysis patients (4). In patients who receive hemodialysis for a long period of time, hypotension is associated with higher mortality risks. Therefore, recognizing factors that are involved in the reduction of blood pressure during hemodialysis and removing their effects can be helpful in reducing mortality among hemodialysis patients (5).

### Objectives

Considering that the use of PPI is common among hemodialysis patients and that the metabolism of magnesium is disrupted in patients with kidney failure (6), this study was undertaken with the aim of determining the effects of pantoprazole (PPI) and ranitidine (H<sub>2</sub> blocker) on patients' serum magnesium level as well as their relationship with hypotension during hemodialysis.

### Patients and Methods

#### Study protocol

In this double-blind clinical trial, all of the hemodialysis patients in the dialysis unit of Buali hospital, Ardabil who had received hemodialysis for at least six months and had experienced hypotension during the treatment (SBP<90 mm Hg) entered the study. In fact, census sampling technique was used to select the patients to be investigated in the study. Written informed consent form was obtained from each patient before the study. The patients were then randomly assigned to two different groups by receiving closed packets labelled as either A (containing ranitidine (150 mg) and pantoprazole placebo (40 mg)) or B (containing pantoprazole (40 mg) and ranitidine placebo (150 mg)). The patients used these medications in the mentioned doses for three months on a daily basis. Both before the intervention and after that, venous blood samples (3 cc) were taken from each of the patients in order to assess their serum magnesium level. Additionally, during dialysis, their blood pressure was monitored each hour and the obtained values were recorded in their file. Based on the hourly values of blood pressure, the mean blood pressure in each hemodialysis session was calculated for each of the patients. Then their mean blood pressure was also calculated for each month until the end of the

study. The exclusion criteria were suffering from chronic diseases like cancer, having serum magnesium level of lower than 1.6 mg/dL, and using antihypertensive drugs. In this study, paired *t* test was used both before and after the intervention to analyze the obtained data and test the hypothesis. Independent *t* test was also employed to compare the means of the two groups in different variables.

#### Ethical issues

The research was conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Ardabil University of Medical Sciences approved the study. The institutional ethical committee at Ardabil University of Medical Sciences accepted all study protocols (IR.ARUMS.REC.1398.295). Accordingly, written informed consent was taken from all participants before any intervention. The trial protocol was approved in the Iranian Registry of Clinical Trials identifier: IRCT20150808023559N19; <https://en.irct.ir/trial/42478>). This study was extracted from MSc/MD thesis of Elham Saeedi at this university (Thesis#0155).

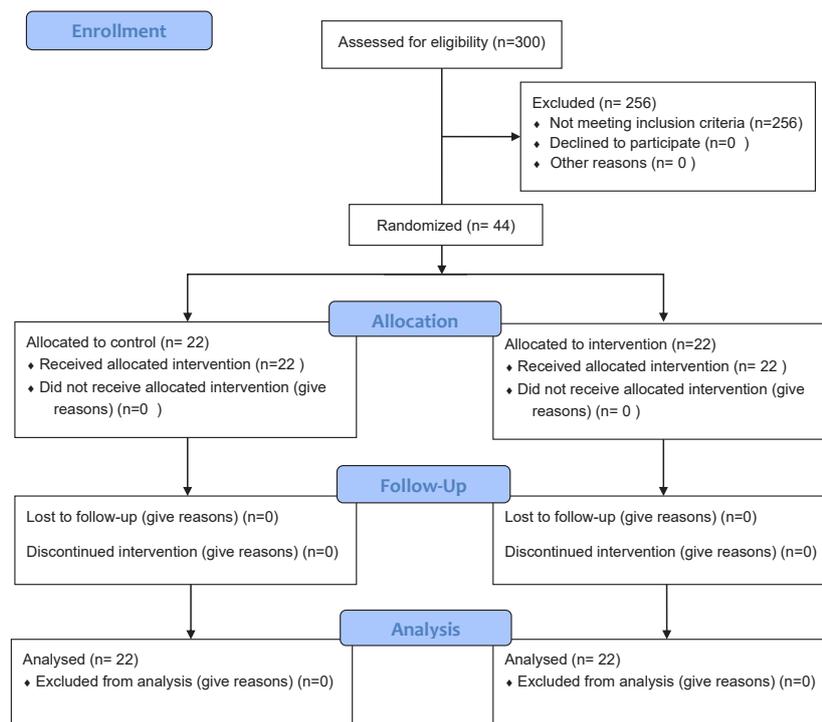
#### Data analysis

All of the statistical analysis was performed using SPSS Software, version 19. The significance level for all of the tests was set at 0.05 and all of the results were reported in the form of mean ± standard deviation.

### Results

In this study, 44 hemodialysis patients were investigated (Figure 1). The mean age of the patients was 60.14±12.98 years. Around 63.6% of the total patients were female. The patients' average length of dialysis was 4.5±3.31 years. The analysis of diastolic blood pressure at the beginning and at the end of the intervention indicated that in the group of patients receiving pantoprazole, the post-dialysis diastolic blood pressure reduced significantly at the end of the study as compared to the beginning of the study. However, such difference was not observed in the case of systolic blood pressure (Table 1).

In the group of patients who received ranitidine, serum magnesium level was 1.00±0.15 mg/dL at the beginning of the study and 0.98±0.13 mg/dL at the end of the study. However, the resulting difference was not found to be statistically significant. On the other hand, in the group of the patients who received pantoprazole, serum magnesium level was 1.02±0.12 mg/dL at the beginning of the study and 0.92±0.92 mg/dL at the end of the study. Contrary to the case of patients receiving ranitidine, the resulting difference in this group of patients turned out to be statistically significant (Table 2).



**Figure 1.** Flowchart of the study.

## Discussion

Hypotension is the most common side effect of hemodialysis. Its prediction and early prevention can improve ESRD patients' quality of life to a considerable extent. In the present study, diastolic blood pressure in the group of patients receiving pantoprazole reduced significantly at the end of the intervention as compared to the beginning of the study. Moreover, serum magnesium level in this group of patients decreased significantly at the end of the study as compared to the beginning of the study. The most important finding of the present study was that a significant relationship was observed between

the use of PPI and hypomagnesemia.

Hypomagnesemia was first recognized as one of the side effects of using PPI in 2006. Later in 2011, Food and Drug Administration (FDA) also announced that PPI use can lead to hypomagnesemia (7). Many instances of PPI-induced hypomagnesemia have been reported to date the reason for which might be the reduction occurring in the intestinal reabsorption of magnesium (8). This is in line with the finding of the current study regarding the reduction of serum magnesium level in the group of patients receiving pantoprazole.

In their study which was conducted on 7731 subjects

**Table 1.** Variations of blood pressure at the beginning and at the end of the study in the groups under investigation

Variables	Measurement stage	Pantoprazole group (n=22)	Ranitidine group (n=22)	P value	
Systolic blood pressure (mm Hg)	Before hemodialysis	1 <sup>st</sup> month	11.73±0.88	11.59±0.85	
		2 <sup>nd</sup> month	11.41±0.66	11.59±0.73	0.268
		3 <sup>rd</sup> month	11.32±0.78	11.36±0.49	
	After hemodialysis	1 <sup>st</sup> month	10.95±0.78	10.86±1.04	
		2 <sup>nd</sup> month	10.59±0.80	10.82±1.01	0.659
		3 <sup>rd</sup> month	10.82±1.05	10.36±0.79	
Diastolic blood pressure (mm Hg)	Before hemodialysis	1 <sup>st</sup> month	7.82±0.59	7.68±0.57	
		2 <sup>nd</sup> month	7.45±0.74	7.73±0.55	0.439
		3 <sup>rd</sup> month	7.5±0.80	7.55±0.60	
	After hemodialysis	1 <sup>st</sup> month	7.68±0.57	7.32±0.78	
		2 <sup>nd</sup> month	7.23±0.68	7.55±0.60	0.790
		3 <sup>rd</sup> month	7.04±0.90	7.11±0.92	

**Table 2.** Mean serum magnesium levels in the groups under investigation

Variables	Measurement stage	Pantoprazole group (n=22)	Ranitidine group (n=22)
Serum magnesium (mg/dL)	At the beginning	1.02±0.12	1.00±0.15
	At the end	0.92±0.09	0.98±0.13
<i>P</i> value		0.001*	0.53

Notes: \**P* < 0.05 in paired sample *t* test vs baseline. The data are presented as mean ± SD.

with the aim of exploring the role of magnesium intake on patients' hypotension, Peacock et al indicated that lower level of magnesium might play a part in the occurrence of hypotension in hemodialysis patients. However, they did not observe a significant relationship between high levels of magnesium intake and high systolic blood pressure (9). In our study too, no significant relationship was observed between serum magnesium level and systolic blood pressure. Therefore, our finding in this regard is consistent with their findings.

Similar to our study, Mikolasevic et al investigated 418 subjects to explore the relationship between the use of PPI and serum magnesium level as well as the possible correlation between PPI use and the increased risk of cardiovascular diseases in chronic hemodialysis patients. Their findings revealed that serum magnesium level in patients using PPI was significantly lower than that of the patients who did not use PPI. Their study also indicated a significant correlation between the use of PPI and lower serum magnesium levels in hemodialysis patients (10), which is consistent with the findings of the present study.

Nakashima et al studied 1189 hemodialysis patients with the aim of exploring the relationship between the use of PPI and serum level of magnesium. They found that serum magnesium level in patients using PPI was significantly lower than that of the patients using histamine receptor antagonists or other types of acid suppressing drugs. They also observed that the use of PPI was associated with higher risks of hypomagnesaemia in hemodialysis patients (11).

In another study whose findings are consistent with the findings of the present research, Ago et al investigated 339 hemodialysis patients with the aim of exploring the role of hypomagnesemia and PPI use on the mortality of these patients. Their results showed that serum magnesium level in patients using PPI was lower than that of the patients who did not use PPI, which was indicative of a significant relationship between the use of PPI and serum magnesium level. According to their findings, serum magnesium level is lower in patients using PPI; and in inflammatory state, low serum magnesium level is considered as a significant predictor of mortality among hemodialysis patients (12).

The mechanism of PPI-associated hypomagnesemia is not completely clear. What is known is that when the oral consumption of magnesium decreases, the active

intestinal absorption of magnesium usually increases due to the activation of TRPM6 and TRPM7 channels and this, in turn, corrects hypomagnesemia when oral and intestinal absorption of magnesium decreases (13). Recently, it has been found that PPI disrupts the intestinal absorption of magnesium by disrupting its active transfer via TRPM 6/7 channels (13) and thereby disrupts the intestinal adaptive response to the reduction in the dietary intake of magnesium. It seems that this mechanism occurs with a decrease in intestinal pH which reduces the affinity of TRPM 6/7 to magnesium and thereby disrupts its absorption (14).

In the present study, diastolic blood pressure in patients receiving pantoprazole decreased significantly at the end of the study as compared to the beginning of the study. In order to reveal the possible effects of PPI use on blood pressure, Joya et al, investigated the blood pressure of patients using PPI as well as those not using PPI with 24-hour blood pressure Holter monitoring (15). They found that both systolic and diastolic blood pressures reduced with the use of PPI. In the case of diastolic blood pressure, their findings were consistent with the findings of the present study. However, as regards systolic blood pressure, their findings were not in line with ours as we did not observe any significant relationship between this type of blood pressure and PPI use. The reason for this lack of relationship in our study might be the shorter duration of the investigation. Maybe, if the investigation lasted longer, the effect of hypomagnesemia on the reduction of blood pressure could be revealed.

**Conclusion**

Serum magnesium level in the patients receiving pantoprazole was significantly lower than that of the patients receiving ranitidine. The use of PPI was found to be an independent and strong predictor of low-concentration of magnesium. In this study, a significant relationship was observed between the use of PPI and low-serum magnesium levels in hemodialysis patients. It was also observed that pantoprazole significantly reduces diastolic blood pressure.

**Limitations of the study**

One of the important limitations of the current study was the investigation of a limited number of patients.

Another important limitation was the short duration of the intervention.

### Suggestions for further research

In order to further consolidate these findings, it is recommended that this study be replicated with larger sample sizes. Prospective studies are also required in the future to find a replacement for magnesium in hemodialysis patients who use PPI.

### Authors' contribution

SMK, ES and SM were the principal investigators of the study. SMK, SM, FP, SH and ES were included in preparing the concept and design. SM and SMK revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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