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Original Research Paper

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RELATIONSHIP BETWEEN SERUM MAGNESIUM LEVELS WITH INTRADIALYTIC HYPERTENSION IN REGULAR HEMODIALYSIS PATIENTS

Filsi Elsa Novenda — Division of Nephrology Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Sumatera Utara/Adam Malik General Hospital Medan, Indonesia

Alwi Thamrin Nasution* — Division of Nephrology Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Sumatera Utara/Adam Malik General Hospital Medan, Indonesia *Corresponding Author

Syafrizal Nasution — Division of Nephrology Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Sumatera Utara/Adam Malik General Hospital Medan, Indonesia

ABSTRACT

Introduction: Intradialytic hypertension (IDH), one of cardiovascular complications of hemodialysis, is reported in around 5-15% of patients undergoing regular hemodialysis (HD). Etiology including subclinical fluid excess, sympathetic overactivity, activation of the angiotensin renin system, endothelial cell dysfunction, and specific dialytic techniques. Imbalances in endothelial derivative hormones, such as nitric oxide and endothelin-1, are also causes of IDH. One of the treatments proposed is by manipulating the composition of the dialysate, such as the concentration of magnesium (Mg). Mg dialysate concentration is known to affect intradialytic blood pressure by changing vascular tone so that it could change blood pressure.

Method: This study was an analytical cross-sectional study to determine the relationship between magnesium levels and intradialytic hypertension in regular HD patients (≥ 3 months) aged> 18 years in the hemodialysis unit of General Hospital of Haji Adam Malik Medan. After obtaining approval from the ethics committee and giving informed consent, a magnesium level examination of the subject was conducted after hemodialysis process. Then pre-dialysis and durante dialysis blood pressure were measured. After the full data is collected, data processing and data analysis are conducted.

Results: Of the 78 subjects, patients with intradialytic hypertension experienced hypomagnesemia of 63.3%, while patients with intradialytic hypotension experienced hypermagnesemia of 61.9%.

Conclusion: There is a significant relationship between serum magnesium levels and intradialytic hypertension in regular hemodialysis patients (p = 0.001) with Mg levels as low as <1.6 mg / dl can affect intradialytic hypertension in regular hemodialysis patients (r=-0,502). Hypomagnesemia has a risk of 3.45 times greater of having intradialytic hypertension compared to a person with intradialytic hypotension or normotension during dialysis.

KEYWORDS : Hemodialysis, Intradialytic Hypertension, Magnesium

INTRODUCTION

Hemodialysis (HD) is still the main renal replacement therapy where there are more than two million patients currently undergoing HD throughout the world.[1] One of the important intradialytic complications to evaluate is cardiovascular complications in the form of cardiac arrhythmias, sudden death, intradialytic hypotension and intradialytic hypertension.[2] Intradialytic hypertension (IDH) is reported in around 5–15% of patients undergoing regular HD with etiology including subclinical fluid excess, sympathetic overactivity, activation of the angiotensin renin system, endothelial cell dysfunction, and specific dialytic techniques. Imbalances in endothelial derivative hormones, such as nitric oxide (NO; smooth muscle vasodilator) and endothelin-1 (vasoconstrictor) are also causes of IDH. One of the treatments proposed is by manipulating the composition of the dialysate, such as the concentration of magnesium (Mg). Mg dialysate concentration is known to affect intradialytic blood pressure.[3]

Mg is reported to be involved in regulation of blood pressure where Mg can change vascular tone result in increased blood pressure.[4] Mg serum is associated with endothelial dysfunction, increased reactivity, increased contractility, vascular remodeling and inflammation, and increased blood pressure.[5]

In a study conducted by Ma et al., hypomagnesium was associated with increased blood pressure.[6] The ARIC study revealed that serum Mg levels were inversely related to systolic blood pressure.[7] Furthermore, a meta-analysis involving about 2000 people revealed that Mg supplementation was associated with decreased blood pressure.[8] Based on the information above and due to no data regarding the relationship of serum Mg levels with intradialytic hypertension in recent days, the authors are interested in conducting this study.

METHOD

STUDY SAMPLE

The samples of this study were all patients with chronic kidney disease who underwent regular hemodialysis in the hemodialysis unit of the General Hospital of Haji Adam Malik Medan who had undergone regular hemodialysis for ≥ 3 months, were aged> 18 years, and had received information and gave consent to participate in voluntary and written research. Patients who did irregular hemodialysis (not routinely undergoing 2 times hemodialysis within 1 week) were excluded from this study.

STUDY DESIGN

This study is an analytical cross-sectional study to determine the relationship between magnesium levels and intradialytic hypertension in regular hemodialysis patients conducted in May 2018. After obtaining approval from the ethical committee, subjects who met the inclusion and exclusion criteria were given an explanation and are asked to give written informed consent to take part in the research. Then blood samples of the subjects were taken for examination of magnesium levels after hemodialysis. Next, pre-dialysis and durante dialysis blood pressure of the patients were measured. After the data was collected, data processing and data analysis were then conducted.

STATISTICAL ANALYSIS

Univariate analysis is performed to obtain an overview of each variable studied, both the independent variable and the dependent variable.

Bivariate analysis is used in analysis of two variables; the dependent variable and the independent variable. The bivariate analysis used is chi square test because the independent variable is nominal data and the dependent variable is nominal data. Whereas the average difference analysis of more than two groups used the one way annova test with an alternative test of kruskal wallis and the Mann Whitney post hoc test. Variable correlation analysis with numerical measuring scale between magnesium levels and systolic blood pressure using Pearson correlation test with spearman alternative test if the data are not normally distributed.

RESULTS

Characteristics of Research Subjects

This study was participated by 78 people with the majority of subjects were male (74.4%), and median age of 55 years. The majority educations of subjects are junior high school (32.1%), work as entrepreneurs (46.2%), and are married (85.9%). (Table 1)

Based on the results of laboratory tests, the median magnesium level is 1.87 mEq / ml. Normal magnesium levels were found in 27 patients (34.6%), hypomagnesium in 30 patients (38.5%), and hypermagnesium in 21 patients (26.9%). The subjects were divided into 3 groups based on durante dialysis blood pressure into intradialytic normotension, hypotension, and hypertension. Each groups consisting of 26 subjects.

Table 1 Study Subjects Characteristics

Characteristics	N=78
Sex,n (%)	
Male	58 (74,4)
Female	20 (25,6)
Age (Years), Median (Min-Max)	55 (20 – 77)
Marriage Status, n(%) Married Not Married	67 (85,9) 11 (14,1)
Laboratory Test Result	
Magnesium, Median (Min-Max)	1,87 (1,25-2,96)
Magnesium, n(%)	
Normal	27 (34,6)
Hypomagnesium	30 (38,5)
Hypermagnesium	21 (26,9)
Durante Dialysis Blood Pressure, n(%)	
Normal	26 (33,3)
Hypotension	26 (33,3)
Hypertension	26 (33,3)

a. Descriptive Numeric (normal data distribution, Mean±S.D)
b. Descriptive Numeric (abnormal data distribution, Median (Max-Min))

Table 2 Characteristics of Research Subjects to Intradialytic Blood Pressure

Characteristics	Intradialytic Blood Pressure		
	Normotension (n=26)	Hypotension (n=26)	Hypertension (n=26)
Sex,n (%)			
Male	22 (84,6)	16 (61,5)	20 (76,9)
Female	4 (15,4)	10 (38,5)	6 (23,1)
Age	46,73±15,44	53,88±12,93	52,92±11,44
Status, n(%)			
Married	19 (73,1)	24 (92,3)	24 (92,3)
Not Married	7 (26,9)	2 (7,7)	2 (7,7)
Laboratory Result			
Magnesium	2,04±0,38	1,98±0,39	1,71±0,40

Differences between Laboratory Results and Intradialytic Blood Pressure

Bivariate analysis was used to see differences in magnesium laboratory results. Normally distributed data is analyzed by one way annova test, and an alternative test of Kruskal wallis used on not normally distributed data. From the results of bivariate analysis it was found that there were significant differences in magnesium levels on intradialytic blood pressure ($p < 0.05$) (Table 3)

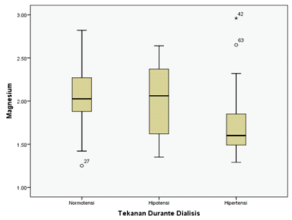
Table 3 Differences in Magnesium Levels and Intradialytic Blood Pressure

Laboratory Result	Intradialytic Blood Pressure			p
	Normotension	Hypotension	Hypertension	
Magnesium	2,04±0,38	1,98±0,39	1,71±0,40	0,008 [a]

a. Annova Test b. Kruskal Wallis Test

Picture 1 Boxplot Diagram of Magnesium with Intradialytic Blood Pressure

Picture 1 Boxplot Diagram of Magnesium with Intradialytic Blood PressurePP



Picture 1. Boxplot Diagram of Magnesium with Intradialytic Blood Pressure

Table 4 is a Post Hoc test between intradialytic blood pressure group and differences in statistically significant magnesium levels between intradialytic normotensive groups compared with intradialytic hypertension group ($p = 0.011$). However, in this study there was no difference in magnesium levels between the intradialytic normotensive group compared with intradialytic hypotension, and between intradialytic hypotension group with the intradialytic hypertension group ($p > 0.05$).

Table 4 Post Hoc Test: Intradialytic Blood Pressure Group to Magnesium Level

Magnesium	P*
Normotension vs Hypertension	0,011
Normotension vs Hypotension	1,000
Hypotension vs Hypertension	0,051

Effect of Intradialytic Blood Pressure on Magnesium Serum Levels

Serum magnesium levels are divided into hypomagnesemia (<1.6 mg / dl), normomagnesemia (1.6 - 2.6 mg / dl), and hypermagnesemia (> 2.6 mg / dl). Table 5 shows a statistically significant relationship between increased intradialytic blood pressure and magnesium levels ($p=0.001$). Patients with intradialytic hypertension experienced hypomagnesemia of 63.3%, while patients with intradialytic hypotension experienced hypermagnesemia of 61.9%. From table 3 it can be concluded that an increase in intradialytic blood pressure will reduce serum magnesium levels while a decrease in blood pressure causes an increase in serum magnesium levels in dialysis patients.

Table 5 Effect of Intradialytic Blood Pressure on Magnesium Serum Levels

		Magnesium Level (mg/dl)						p
		Hypomagnesemia		Normal		Hypermagnesemia		
		N	%	N	%	N	%	
Intradialytic Blood Pressure	Normotension	6	20,0%	15	55,6%	5	23,8%	0,001[a]
	Hypotension	5	16,7%	8	29,6%	13	61,9%	
	Hypertension	19	63,3%	4	14,8%	3	14,3%	
	Total	30	100,0%	27	100,0%	21	100,0%	

a.Chi Square Test

In table 6, based on the Spearman correlation analysis test, the correlation of systolic blood pressure and magnesium levels has a moderate relationship with a negative correlation direction (r = -0,502). Increasing intradialytic blood pressure increased magnesium levels. Based on the calculation of the prevalence ratio of patients with hypomagnesemia, there are 3.45 times greater risk for experiencing intradialytic hypertension compared to subjects with intra-dialytic hypotension or normotension after dialysis. (Table 7)

Table 6 Correlation Test of Systolic Blood Pressure Against Magnesium Levels

	R	p*
Blood Pressure Intradialysis*Magnesium Level	-0,502	<0,001

Table 7 Relationship of Intradialytic Blood Pressure with Magnesium Serum Levels

		Magnesium Level(mg/dl)					
		Hypomagnesemia		*Normo-Hypermagnesemia*		Total	
		N	%	N	%	N	%
Intradialytic Blood Pressure	Hypo-normotension	11	36,67	41	85,42	52	100
	Hypertension	19	63,33	7	14,58	26	100
	Total	30	38,46	48	61,53	78	100

$$\text{Prevalens Ratio} = \frac{\textit{Hypertensive Hypomagnesemia Prevalence}}{\textit{Hypertensive Not hipomagnesemia Prevalence}} = \frac{19/26}{11/52} = \frac{0,730}{0,211} = 3,45$$

DISCUSSION

This study were participated by 78 patients consisting of 26 patients with intradialytic hypertension, 26 patients with intradialytic hypotension, and 26 patients with intradialytic normotension. The majority of patients with intradialytic hypertension were male (76.9%), with an average age of 52.92 ± 11.44 years. The study of Nilrohit Paike et al., Kandarina Yenny et al., and Abbasi Mohammadreza et al. reported no significant association between age and sex in patients with intradialytic hypertension.[9,10]

From the results of the study, there was a statistically significant relationship between intradialytic hypertension with magnesium levels (p = 0.001). This is in line with the report of Kyriazis Jhon et al. study using different dialysates with 4 different groups, in group 4 (dialysate Mg. 25mmol / L, dialysate Ca1.25mmol / L) significant relationship was found between decreased serum magnesium levels after hemodialysis and intradialytic hypertension (p = .001).[11] Patients with intradialytic hypertension had hypomagnesemia of 63.3%, while patients with intradialytic hypotension experienced hypermagnesemia of 61.9%. Increased intradialytic blood pressure will reduce serum magnesium levels while decreasing intradialytic blood pressure causes a decrease in serum magnesium levels in dialysis patients. The correlation of systolic blood pressure to magnesium levels has a moderate relationship with a negative correlation direction (r = -0,502). The etiology of multifactorial intradialytic hypertension includes subclinical fluid excess, sympathetic overactivity, activation of the angiotensin renin system, endothelial cell dysfunction, and specific dialytic techniques.[12]

At the vascular level, decreased Mg is associated with endothelial dysfunction, increased reactivity, increased contractility, vascular and inflammatory remodeling, and increased blood pressure. Maryam et al. stated that an increase in Mg levels was associated with vasodilation, anti-inflammatory response, and decreased blood pressure. Other studies have shown a significant reduction in serum Mg levels during dialysis, and appear to be lower during dialysis.[5] Misra Paraish et al. found that patients with low serum Mg levels (<1.3 mg / dl) had a high risk of death. [13] While Maryam Pakferat et al. showed significant hypomagnesemia (p = 0.02) during dialysis in patients with intradialytic hypotension, [5] this was different with this study result where intradialytic hypertension was statistically significant with hypomagnesemia (p <0.001).

Bilal Javaid et.al compare serum magnesium levels in patients who had normal blood pressure versus hypotensive during dialysis. It is showed that magnesium values were 2.22 ± 0.21 in patients with normal blood pressure and 1.68 ± 0.11 in hypotension patients during the analysis.[14] While Alhosaini et al. reported that of 62 patients who underwent regular hemodialysis in a hospital in America, 39% of them had hypomagnesium.[15] Hypomagnesium alone was found to be associated with poor outcomes, including in patients who had undergone regular hemodialysis.[13] Misra Paraish et al. also began to look for a relationship between the use of proton pump inhibitors (PPIs) and hypomagnesemia in hemodialysis patients, although this theory was still in debate.[13] Up until now there are still unanswered questions about magnesium level balance and its effects on patients with chronic kidney disease and dialysis patients.[16]

Based on this study, the calculation of the prevalence ratio of patients with hypomagnesaemia was 3.45 times greater at risk for experiencing intradialytic hypertension compared to subjects with intradialytic hypotension or normotension during dialysis. There is no data obtained about the prevalence of magnesium levels in patients with intradialytic hypertension. Hypomagnesaemia plays a role in the pathogenesis of hypertension, endothelial dysfunction, dyslipidemia, and inflammation associated with arterial stiffness.[17] Previously Noel Peter et al. showed that patients with reduced systolic blood pressure of at least 10 mmHg from pre-dialysis to post-dialysis compared with increased blood pressure increase have a higher chance ratio for hospitalization or death after 6 months.[18] Inrig JK et al. reported patients with reduced survival in intradialytic hypertension compared to patients with low blood pressure in other studies for 2 years.[19] A cohort study of Fly the Jennifer et al reported more than 100,000 hemodialysis patients with a decrease in systolic blood pressure of 14 mm Hg, followed for more than 5 years, have better survival.[20]

CONCLUSION

The conclusion of this study is that there is a significant relationship between serum magnesium levels and intradialytic hypertension in regular hemodialysis patients (p=0.001) and the level of hypomagnesemia as low as Mg <1.6 mg / dl can affect intradialytic hypertension in regular hemodialysis patients (r=-0,502). The prevalence of patients who have hypomagnesemia is 3.45 times greater at risk for experiencing intradialytic hypertension compared to someone with intradialytic hypotension or normotension during dialysis.

SUGGESTION

Future research needs to emphasize the sample sizes and do more detailed assessments of blood pressure checks at each dialysis session, conduct a before and after dialysis magnesium examination, history anti-hypertensive drugs use, previous history, duration of HD, and other comorbidities that were not evaluated in this research.

REFERENCES

1. Suhardjono. Hemodialisis : Prinsip dasar dan pemakaian kliniknya. In: Buku Ajar Penyakit Dalam. 6th ed. 2014. p. 2192-6.
2. Teta D. Intradialytic complications. 40th Annual Meeting of The Swiss Society of Nephrology; 2008 Dec 3-5; St.Gallen (Swiss).
3. Liu F, Xintian Z, Qi Het al. Corellation of serum magnesium with cardiovascular risk factor in maintenance hemodialysis patients. Magnesium Research 2013;26(3):100-8.
4. Grober U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients 2015;7:8199-8226.
5. Pakfetrat M, Roozbeh J, Malekmakan N, Nasab M, Nikoo M.. Is there an association between intradialytic hypotension and serum magnesium changes?. Hemodialysis International 2010;14:492-497.
6. Rodriguez M, L.M.de Francisco A. Magnesium : its role in CKD. Nefrologia. 2013;33(3):389-99.
7. Ma J, Folsom A, Melnick S, Eckfeldt J, Sharrett A, Nabulsi A. Associations of serum and diatery magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness L the ARIC study. Atherosclerosis Risk in Communities

Study, J Clin Epidemiol 1995;48:927-40.
8. Jee S, Miller R, Guallar E, Sing V, Appel L, Klag M. The effect of magnesium supplementation on blood pressure: a meta analysis of randomized clinical trials. Am J Hypertens 2002;15:691-6 .
9. Yenny K, Ketut S, Raka W.Excessive Ultrafiltration During Hemodialysis Plays a Role in Intradialytic Hemodialysis Through Serum Nitric Oxide (NO) Level. The Open Urology & Nephrology Journal. 2018; Vol 11:61-71.
10. Mohammadreza A, Bahareh H. The Main Determinants of Intradialytic Hypertension During Dialysis in Chronic Hemodyalisis patients; A Singel Center Study. J Renal Inj Prev.2018;7(3):152-159.
11. Kyriazis J, Kalogeropoulou K, Bilirakis L, et al. Dialysate magnesium level and blood pressure. Kidney Int. 2004; 66:1221–1231.
12. Jula K, Ingrid MD, MHS. Intradialytic Hypertension: A less-recognized cardiovascular complication of hemodialysis. Am J Kidney Dis 2010 March; 55(3):580-589.
13. Misra P, Alam A, Lipman M, Nessim S. The relationship between proton pump inhibitor use and serum magnesium concentration among hemodialysis patients. BMC Nephrology. 2015;16:136.
14. Javaid B, Adil N, Farooq MU. Frequency of Intradialytic Hypotension and Comparison of Serum Magnesium Levels in Patients Having Normal Blood Pressure During Dialysis Session Versus Patients Developing Hypotension During Dialysis. APMC 2018;12(3):223-5.
15. Fulop T. Hypomagnesemia. Medscape 2016.
16. Cunningham J, Rodriguez M, Messa P. Magnesium in chronic kidney disease stages 3 and 4 and in dialysis patients. Clin Kidney J.2012;5(suppl 1):i39-i51.
17. Steven VL, Celline, Francis et al. The relation hypomagnesemia and vascular stiffness in renal transplant recipients. Nephrol Dial Transplant 2011;26:2362-2369
18. Peter N, Jula K. Mechanisms and Treatment of Intradialytic Hypertension. Blood Purif. 2016;41:188–193
19. Inrig JK, Uptal DP, Robert DT, Lynda AS. Association of Blood Pressure Increases During Hemodialysis With 2-Year Mortality in Incident Hemodialysis Patients: A Secondary Analysis of the Dialysis Morbidity and Mortality Wave 2 Study.Am J Kidney Dis. 2009; 54(5): 881–890.
20. Flythe J, Hui Xue,Katherine EL,Gary C,Steven M.Association of Mortality Risk with Various Definitions of Intradialytic Hypotension.J Am Soc Nephrol.2015; 26: 724–734.