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Research Article

EFFECT OF THIAZIDE AND LOOP DIURETICS ON SERUM MAGNESIUM AND OTHER ELECTROLYTES IN CARDIAC PATIENTS

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ABSTRACT

Diuretics are agents that promote diuresis and are widely used for various indications like hypertension, edema of cardiac, renal failure or liver cirrhosis, acute pulmonary edema. Despite its key role, diuretics can have serious side effects like volume depletion and electrolyte disorders, with greater relevance in ageing population. Thiazide and loop diuretics have shown to cause alterations in serum magnesium and other electrolyte levels resulting in fatal complications like ventricular arrhythmias, coronary artery vasospasm or sudden death. This severely affects the quality of life of the patient especially those with cardiac illness. By this study we aim at reinforcing the importance of magnesium supplementation and the importance of including serum magnesium among the frequently monitored parameters, in the cardiac department.

Keywords: thiazide diuretics, loop diuretics, electrolytes, hypomagnesemia, arrhythmia

INTRODUCTION

Diuretics are agents that cause production of urine by promoting excretion of salt and water from the kidneys. Diuretic are classified into loop diuretics, thiazide diuretics, potassium sparing diuretics, carbonic anhydrase inhibitors and osmotic diuretics. Diuretics are widely used for indications like hypertension, edema of cardiac, renal failure or liver cirrhosis, acute pulmonary edema. The mechanism of action of each class of diuretic is specific, based on the site of their action.

Loop diuretics prevent reabsorption of sodium and chloride ions in the loop of Henle by exerting their diuretic action on Na(+)-K(+)-2Cl(-) cotransporter in the thick ascending limb.This class includes furosemide, bumetanide, torsemide. Thiazide diuretics inhibits sodium reabsorption by inhibiting the Na(+)-Cl(-) cotranspoter in the distal convoluted tubule.This class includes chlorthiazide, chlorthalidone, hydrochlorothiazide, indapamide, metalazone.

Diuretics have shown to influence serum electrolyte levels causing alterations in, sodium potassium, magnesium, and calcium.

Magnesium is the second most abundant intracellular cation after potassium. It plays a key role in a variety of enzymatic reactions, energy-requiring metabolic processes and anaerobic phosphorylation, protein and DNA synthesis as well as in transmembrane transport mechanisms.

Normal range: 0.7-1 mmol/L; 1.7-2.4mg/dl

Hypomagnesemia and depletion of intracellular stores, especially in cardiac muscle, have been responsible for a variety of cardiovascular and other functional abnormalities. These may include various arrhythmias, such as atrial fibrillation and torsade de pointes, impairment of cardiac contractility and vasoconstriction.

Sodium is equally important for heart function and is needed for voltage gated sodium channels in the outer membranes of cardiac cells. It is important for

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initiating the action potential and triggering contractions of cardiac muscle fibres.
Normal range: 135-145 mEq/L
Potassium is an electrolyte which is crucial to heart function and plays a key role in skeletal and smooth muscle contraction as well as conduction of electric impulses in the body. It also has a role in regulating blood pressure. Its deficiency (hypokalemia) can cause weakness as cellular processes are affected.
Normal range- 3.5 – 5.0mmol/L
Calcium ions play an important role in activating muscle contractile process. An excess of calcium ions cause spastic contractions whereas its deficiency causes cardiac flaccidity.
Normal range: 8.5-10.2mg/dL

METHODS AND MATERIALS:

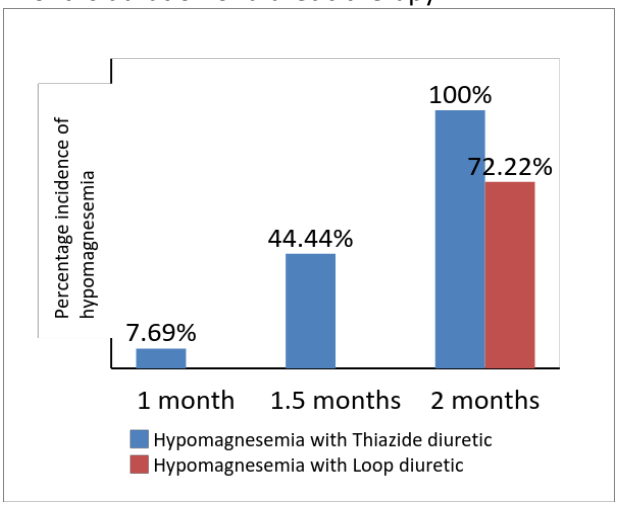
A prospective, experimental study was conducted in Department of Cardiology at Pushpagiri Medical College Hospital, on the topic "Effect of Thiazide and Loop Diuretics on serum Magnesium and other electrolytes in Cardiac patients". The study was carried out after getting approval from Institutional Ethics Committee. The selection of patients was based upon the inclusion and exclusion criteria. A written Informed Consent was obtained from the patient or care-giver.

Patients who had been on thiazide or loop diuretics for a period of one to two months were identified and demographic details of the patients were collected and recorded. The residual blood of the participants involved in the study, were collected from the Biochemistry laboratory and analyzed for serum magnesium, using semi-auto analyzer in Pushpagiri College of Pharmacy. The values of other electrolytes were obtained from the patient's routine lab test results. These values were analysed statistically using Chi-square analysis compared to that of age-matched control subjects. The quality of life of patients taking diuretics were also determined using 'The Quality of Life Enjoyment and Satisfaction questionnaire-short form' (Q-LES-Q-SF).
Procedure for quantitative determination of Magnesium in serum:

- Blank: Pipette 1ml of the Mg reagent to a test tube.
- Standard: Pipette 1ml of the Mg reagent and 10µL of Mg standard (1.04mmol/L) to a test tube.
- Sample Test: Pipette 1ml of the Mg reagent and 10µL of patient's residual serum into a test tube.
- Mix and incubate for 5 minutes at room temperature.
- Read the value of magnesium using semi-auto analyzer.

RESULTS:

The comparative study on the effect of using THIAZIDE and LOOP DIURETICS,on serum magnesium levels showed that the incidence of hypomagnesemia (Mg less than 0.65mmol/L) in patients using THIAZIDE increased progressively with duration of therapy, with all the patients developing hypomagnesemia within 2 months. While in patients using LOOP DIURETICS, hypomagnesemia developed only within 2 months duration of diuretic therapy.



Quality of life decreased with increased age and a good QOL greater than 70% was observed only in patients taking Loop diuretics. QOL also had an inverse association with incidence of hypomagnesemia i.e., patients with poor QOL showed greater incidence of hypomagnesemia and those with good QOL showed no such incidence.

Among electrolyte disturbances, hypomagnesemia was observed in 51.4% of the Thiazide diuretic users and 37.1% of Loop diuretic users. Hypokalemia occurred in 40% in Thiazide users and 42.9% in Loop users. Hyponatremia was seen in 77.1% and 71.4% in Thiazide and Loop diuretic users respectively. Thiazide diuretics showed an incidence of hypocalcemia in 37% and hypercalcemia in 6% of study subjects. Loop diuretics showed an incidence of hypocalcemia in 63% of study subjects. These

electrolyte imbalances were observed in age group 61-70yrs.

PARAMETER	CONTROL	THIAZIDE	LOOP
Mean/Standard deviation			
Age	64 ± 10.61	66.54 ± 10.52	
Serum Magnesium	0.82 ± 0.17	0.71 ± 0.19	0.77 ± 0.34
Serum Calcium	2.08 ± 0.27	2.18± 0.37	1.72 ± 0.54
Serum Sodium	138.1 ± 2.75	132.91 ± 4.85	131.31 ± 5.73
Serum Potassium	3.79 ± 0.18	3.73 ± 0.54	3.71 ± 0.55

Mean age in control and test subjects were found to be similar.

Average serum magnesium was found to be low in both, subjects using THIAZIDE and LOOP diuretics when compared to the average serum magnesium of the control group. Among the exposed group, THIAZIDE diuretic users showed lower mean serum magnesium.

In THIAZIDE users the mean serum calcium was found to be greater than in controls. The opposite was observed with LOOP diuretics.

The mean sodium levels were observed to be lesser than the average value in controls.

Similar pattern was observed with mean potassium values.

DISCUSSION:

Among the 70 cardiac patients enrolled into the study, based on the inclusion and exclusion criteria, 18(51.4%) subjects on Thiazide diuretics and 13(37.1%) subjects on Loop diuretics were found to have hypomagnesemia. This was found statistically significant (p value<0.05) using chi-square analysis.

Hypokalemia was observed slightly more with Loop diuretics.

Hyponatremia developed more frequently with thiazide diuretics.

Loop diuretics showed a greater incidence of hypocalcemia than Thiazide diuretics and cases of hypercalcemia were noted only in Thiazide users.

Incidence of hypomagnesemia increased progressively with duration of therapy while using Thiazide diuretics. Loop diuretics were found to be comparatively safer with no incidence of hypomagnesemia until duration of 1.5 months of therapy.

Hypomagnesemia was however significant within 2 months duration of diuretic therapy for both Thaizide and Loop diuretics.

A greater incidence of hypomagnesemia was observed in patients on Loop diuretics with poor QOL whereas Thiazide diuretics caused greater incidence of hypomagnesemia in patients with fair QOL. However, no incidence of hypomagnesemia was observed in patients with good QOL.

Loop diuretics were associated with better QOL than Thaizide diuretics.

Increased age also showed an inverse correlation with QOL.

CONCLUSION:

Diuretics are a class of drugs commonly prescribed among cardiac patients, despite its serious side effects like volume depletion and induction of electrolyte disorders. Abnormalities like hypomagnesemia and other electrolyte disturbances may result in fatal complications like ventricular arrhythmias or coronary artery vasospasm, thereby causing further deterioration in patient's condition.

From the current study conducted among the cardiac patients in Pushpagiri Medical College Hospital, Thiruvalla, the extent of alteration in serum magnesium levels resulting from Thaizide or Loop diuretics therapy were compared and this deficiency was found to be more associated with Thiazide diuretics. The effect of hypomagnesemia on QOL was evaluated and a greater incidence of the same was associated with poor QOL.

Magnesium-ATP is the main source of energy for the proper functioning of heart. Thus by this study, we also aim at reinforcing the importance of magnesium supplementation in patients with magnesium depletion. Dietary rich sources of magnesium include almonds, yogurt, black bean and spinach.

Through this study, we also ascertain the importance of including serum magnesium among the frequently monitored parameters, in the cardiac department.

REFERENCES:

1. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. - PubMed - NCBI [Internet]. [cited 2017 May 25]. Available from:

https://www.ncbi.nlm.nih.gov/pubmed/10491376

2. Pharmacological Classification and Renal Actions of Diuretics - Abstract - Cardiology 1994, Vol. 84, Suppl. 2 - Karger Publishers [Internet]. [cited 2017 May 26]. Available from: https://www.karger.com/Article/Abstract/176450
3. Use of diuretics in cardiovascular diseases: (1) heart failure | Postgraduate Medical Journal [Internet]. [cited 2017 May 14]. Available from: http://pmj.bmj.com/content/80/942/201
4. Site and mechanism of action of diuretics - The American Journal of Medicine [Internet]. [cited 2017 May 12]. Available from: http://www.amjmed.com/article/S0002-9343(84)80003-0/abstract
5. Heart failure and electrolyte disturbances. - Abstract - Europe PMC [Internet]. [cited 2017 May 25]. Available from: http://europepmc.org/abstract/med/1507935
6. Magnesium Deficiency: A Cause of Heterogenous Disease in Humans - Rude - 1998 - Journal of Bone and Mineral Research - Wiley Online Library [Internet]. [cited 2017 May 26]. Available from: http://onlinelibrary.wiley.com/doi/10.1359/jbmr.1998.13.4.749/full
7. Clinical Physiology of Acid-Base and Electrolyte Disorders - Burton Rose, Theodore W. Post - Google Books [Internet]. [cited 2017 May 26]. Available from: https://books.google.co.in/books/about/Clinical_Physiology_of_Acid_Base_and_Ele.html?id=_eR0BqMxDbIC&redir_esc=y
8. Review article. Magnesium deficiency provoked by diuretics. - PubMed - NCBI [Internet]. [cited 2017 May 27]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/6828948
9. Diuretic induced hyponatraemia in elderly hypertensive women - ProQuest [Internet]. [cited 2017 May 25]. Available from: http://search.proquest.com/openview/bd8361f316322c5c351ba83616ff14b3/1?pq-origsite=gscholar&cbl=35973
10. Diuretic-induced magnesium losses. - Abstract - Europe PMC [Internet]. [cited 2017 May 26]. Available from: http://europepmc.org/abstract/med/6499700
11. Diuretic effects on calcium metabolism. - PubMed - NCBI [Internet]. [cited 2017 May 26]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10598542
12. Effect of thiazides on serum calcium. - PubMed - NCBI [Internet]. [cited 2017 May 26]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=466932%5Buid%5D
13. Furosemide-induced severe hypokalemia with rhabdomyolysis without cardiac arrest | BMC Women's Health | Full Text [Internet]. [cited 2017 May 26]. Available from: https://bmcwomenshealth.biomedcentral.com/articles/10.1186/1472-6874-13-30
14. Effects of diuretics on the renal handling of magnesium. - PubMed - NCBI [Internet]. [cited 2017 May 25]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/6389077
15. Diuretics, Serum and Intracellular Electrolyte Levels, and Ventricular Arrhythmias in Hypertensive Men | JAMA | The JAMA Network [Internet]. [cited 2017 May 26]. Available from: http://jamanetwork.com/journals/jama/article-abstract/395 336
16. Guan Y, Wu X, Xu M, Wu J. [Impact of loop diuretics on blood sodium in patients hospitalized for heart failure]. Zhonghua Xin Xue Guan Bing Za Zhi. 2014 Jul;42(7):582–7.
17. S.P. Chinchilla, I. Urionguena, F. Perez-Ruiz (2015); Serum Magnesium Levels in Patients in Relation To Diuretic Treatment, British Medical Journal, volume 74, Issue supp.2, Pages 112-116
18. N Cohen, D. Almoznino-Sarafian, R Zaidenstein, I Alon, O Gorelik, M Shteinshnaider, *et al.,*(2013); Serum magnesium aberrations in furosemide (frusemide) treated patients with congestive heart failure: pathophysiological correlates and prognostic evaluation, Heart, 2003 – British Medical Journal, Heart 2003;89:411–416
19. Spyridon Arampatzis, Georg-Christian Funk, Alexander Benedikt Leichtle, Georg-Martin Fiedler, Christoph Schwarz, Heinz Zimmermann, *et al*., (2013); Impact of diuretic therapy-associated electrolyte disorders present on admission to emergency department: a cross-sectional analysis, BMC Medicine 2013, 1745-7015/11/83
20. Million HJ, Alexandrides GE, Liberpoulos EN, Bairaktari ET, Goudevenos J, Elisaf MS.(2002); 'Hypomagnesemia and concurrent acid-base and electrolyte abnormalities in patients with congestive heart failure'.European Journal of Heart Failure,Vol 4(2):167-73

21. Ryan MP, Ryan MF, Counihan TB.(1981);'The Effect of Diuretics on Lymphocyte Magnesium and Potassium'.ActaMedScandSuppl;647:153-61

22. van Blijderveen JC,Straus SM,Rodenburg EM, Zietse R, Stricker BH, Sturkenboom MC.*etal., (2014).*'Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide'. American Journalof Medicine;127(8):763-71

23. Rodenburg, Eline M., Visser, Loes E., Hoorn, Ewout J., *et al.,*(2014); Thiazide and the risk of hypokalemia in the general population' , Journal of Hypertension , Volume 32 , issue 10, 2092 – 2097

24. Kuller L, Farrier N, Caggiula A, Borhani N, Dunkle S.(1985).'relationship of diuretic therapy and serum magnesium levels among participants in the multiple risk factor intervention trial'. American Journal of Epidemiology.122(6):1045-59

25. DiaconuCC, BAlaceanu A, Bartos D.(2014); 'Diuretics, first-line antihypertensive agents: are they always safe in the elderly?'.Rom Journal of Intrnal Medicine'52(2):87-90

26. Hollifield JW.,(1986);'Thiazide treatment of hypertension: Effects of thiazide diuretics on serum potassium, magnesium, and ventricular ectopy'.American Journal of Medicine.80(4A):8-12

27. Rejmark,L.,Vestergaard,P.,Pedersen,A.R.,Heicken dorff L.,Andreasen F.and Mosekilde L.(2003) ,Dose-effect relations of loop- and thiazide-diuretics on calcium homeostasis: a randomized double-blinded Latin-square multiple cross-over study in post-menopausal osteopenic women. European Jounal of Clinical Investigation, 33;41-502

28. O.Bryan Holland M.D.,J.V.Nixon M.D., Lavon Kuhnert R. M.(1990), Diuretic-induced ventricular ectopic activity. The American Journal of Medicine, Vol.70.Issue4,762-68