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Original Research Article

Role of serum magnesium in acute exacerbations of chronic obstructive pulmonary disease

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ABSTRACT

Background: This prospective study was done to assess the association between serum magnesium deficiency and its effect on exacerbation of chronic pulmonary obstructive disease (COPD), and also to probably suggest a cut-off level which may be useful for predicting clinical outcomes and serving as a target value for therapeutic intervention.
Methods: This study was conducted among 100 patients in a tertiary hospital, who were diagnosed with COPD, and their serum magnesium levels were measured when they presented to the hospital during routine check-up (stable) and during an exacerbation. Their PEFR and oxygen saturation were also measured to assess severity.
Results: Out of 100 patients studied, 91 were males and 9 were females, of which 38 of them were aged 60 or below and 62 of them aged 61 and above. The average serum magnesium levels of patients presenting during routine check-up was 2.08 mg/dl (below 60) and 2.06 mg/dl (above 61) as compared to values during an exacerbation which was 1.58 mg/dl (below 60) and 1.60 mg/dl (above 60) which was significant. Our study also determined a serum magnesium cut-off value averaging 1.65 mg/dl, which may be useful therapeutic target for intervention.
Conclusions: Serum low serum magnesium levels has a definite association with exacerbations of COPD. Earlier therapeutic interventions may help in decreasing the episodes of exacerbation. A significant reduction of magnesium levels may correlate with severity of airway obstruction.

Keywords: Magnesium, COPD, Exacerbation, PEFR

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a chronic airflow obstruction that is progressive and only partially reversible. It includes spectrum of chronic bronchitis, emphysema and chronic asthmatic bronchitis.[1,2]

Today COPD is recognized as a major killer disease and the fourth most common cause of deaths in the USA.[1]

World health organisation (WHO) predicts that COPD will become the third leading cause of mortality by 2030, owing to decrease in cardiac diseases and stroke over the period of 1970-2002, but the rates of incidence and prevalence of COPD doubled in these years.[12]

Available data suggests there are more than 12 million adults with COPD affection in India with estimated prevalence rates of 2.12 to 9.4% in North India and 1.4 to 4.08% in Southern India. It also associates with a significant economic burden to the nation.[3]

Many studies and researchers have indicated that magnesium deficiency has contributed to exacerbations in COPD and that the treatment with intravenous magnesium in these patients helps in relieving bronchospasm by causing relaxation of bronchial smooth muscle has been proposed.[4-6] The mechanism by which magnesium causes these exacerbations is poorly understood.

Our study uses an observational model, to possibly explore and confirm the association between serum magnesium

levels and its influence over exacerbations of COPD as compared to those at stable COPD conditions.

METHODS

This was a prospective study carried out at Amrita institute of medical sciences, Kochi, Kerala from December 2012-December 2013 (One year).

Study selection criteria

A total 100 patients, irrespective of age and gender and satisfying the inclusion criteria were included in the study, after obtaining their informed consent.

Inclusion criteria (stable COPD patients-patients who come for routine check-up)

Inclusion criteria for stable COPD patients included-patients who come for routine check-up-patients, previously diagnosed to COPD, based on the pulmonary function test (PFT) and GOLD criteria.[7] No exacerbation episodes at least, in the last one month, when presenting to the OPD. Presenting to the OPD for routine COPD status evaluation, with no clinical evidence of exacerbations. Serum magnesium, taken at time of OPD visit, as part of routine investigation panel. Routine oxygen saturation and PEFR values are measured

Inclusion criteria (exacerbation of COPD patients)

Inclusion criteria for exacerbation of COPD patients included-The same patients, satisfying the inclusion criteria for stable COPD patients, who present to the emergency department with clinical symptoms suggestive of an exacerbation of COPD. Clinical symptoms include shortness of breath, severe cough ± cough production. Serum magnesium value taken with routine blood panel, prior to any medical intervention. PEFR and oxygen saturation values are measured on admission.

Exclusion criteria

Exclusion criteria excluded-any change of treatment for COPD within the last 2 weeks, at the time of measurement of magnesium, other lung diseases like tuberculosis, bronchial asthma, lung carcinomas, sarcoidosis, previous history of lung fibrosis, previous histories of lung resections. Patients having a background of chronic kidney diseases, congestive cardiac diseases, uncontrolled type 2 diabetes mellitus are also excluded, as they can interfere with the serum magnesium levels.

Study design and procedure

After including patients in the study as per the inclusion criteria (for both stable COPD and during an exacerbation), serum magnesium values were obtained together with PEFR and oxygen saturation values (to assess severity).

0.5 ml of blood was drawn into a separate Red-top vacutainer and send for serum magnesium assessment. Normal reference values of serum magnesium in our hospital were set between 1.7-2.2 mg/dl. It was measured using the photometric method. PEFR is measured using a standard peak flow-meter.[8-10]

The readings are taken, based on zone measurement, according to the American lung association, into green, yellow and red zones.[8] Oxygen saturation was measured using standard pulse-oximetry.

Informed written consent was obtained from each patient candidate before enrolling them to the study, after explaining in detail about the study protocol in their vernacular language. All information was collected confidentially, without any undue force or pressure.

Ethical approval

Institutional ethical approval obtained.

Statistical analysis

The correlation between outcomes (stable and exacerbations magnesium levels) and the predictor variables was based on logistic regression analysis for which correlation was tested by chi square test. (x^2). Age, data were compared by unpaired t test. Decision levels (cut-offs) for prediction of outcomes were determined by ROC (receiver operator characteristics) curve.

Validity parameters such as sensitivity and specificity, predictive values of positives and negatives and accuracy of cut-off, with respect to clinical criteria will be computed. ROC curve will be drawn to find out an appropriate cut-off point for magnesium with respect to clinical criteria.

Scheffe's post hoc test was used to determine the significance of the outcome variable. Except for the logistic regression, calculations and graphs were computed using the SPSS software (software package for statistical analysis), version 22, released by IBM, and Microsoft office platform, using a personal computer. $P<0.05$ was considered to be statistically significant.

RESULTS

The study sample was constituted by 100 patients, both as outpatient (OP-stable) and when they were admitted during an exacerbation (IP-in patient admission) between December 2012 and December 2013.

Validity parameters such as sensitivity and specificity, predictive values of positives and negatives and accuracy of cut-off, with respect to clinical criteria will be computed. A ROC will be drawn to find out an appropriate cut-off point for magnesium with respect to clinical

criteria. The significant level set by at 0.05 level of significance.

The obtained mean and standard deviation (SD) of magnesium at baseline is (mean 2.07 and SD of 0.10) with a $p<0.05$, and that the corresponding values obtained during an exacerbation is (mean 1.60 with SD of 0.11) and $p<0.05$. Both the values tabulate that values of mean and SD at both the occasions are significant (Table 1).

Table 1: PEFR readings based on zone colour.[8,9]

Zone	Reading	Description
Green zone	80 to 100% of the usual or normal peak flow readings are clear	A peak flow reading in the green zone indicates that the airway status is in good control
Yellow zone	50 to 79% of the usual or normal peak flow readings	Indicates caution. It may mean respiratory airways are narrowing and additional medications may be required.
Red zone	Less than 49% of the usual or normal peak flow readings	Indicates a medical emergency. Severe airway narrowing may be occurring and immediate action needs to be taken. This would usually involve contacting a doctor or hospital.

For patients below 60 years of age, the obtained t-value is 18.80, which is greater than the table value of 1.96 at 0.05 level of significance ($p<0.05$), hence there exists a significant difference between the mean values of magnesium levels measured at baseline and during exacerbations. Also, the mean score of serum magnesium baseline value is 2.08, which is greater than the mean score of magnesium exacerbation value of 1.58. So, it can be concluded that the magnesium baseline values are high in comparison to magnesium values at exacerbation (Table 2).

There exists a significant difference in the baseline magnesium values based on PEFR values and it is clear that patients with PEFR in the green zone have a high magnesium baseline mean score as compared to patients on yellow zone. Table 3 shows the obtained t value is 2.00 which is greater than the table value of 1.96 at 0.05 level of significance ($p<0.05$) for magnesium baseline values on the basis of their PEFR.

However, there exists no significant difference in values of serum magnesium obtained at exacerbation based on PEFR. It also means that patients with PEFR in the red and the yellow zone almost have equal preponderance in exacerbation of COPD. Table 4 shows the obtained t value is 1.80 which is less than the table value of 1.96 at 0.05 level of significance ($p<0.05$) for magnesium values at exacerbation on the basis of PEFR.

According to our study, there exists a significant difference in the magnesium baseline values and those magnesium values obtained at exacerbation. Table 5 shows that the obtained f value is 5.62 which is greater than the table value of 2.47 at 0.05 level of significance ($p<0.05$) for the magnesium baseline score, with relation to magnesium exacerbation mean score. Hence, in order to further strengthen the significance between the two, a Scheffe's post hoc test was used (Table 7).

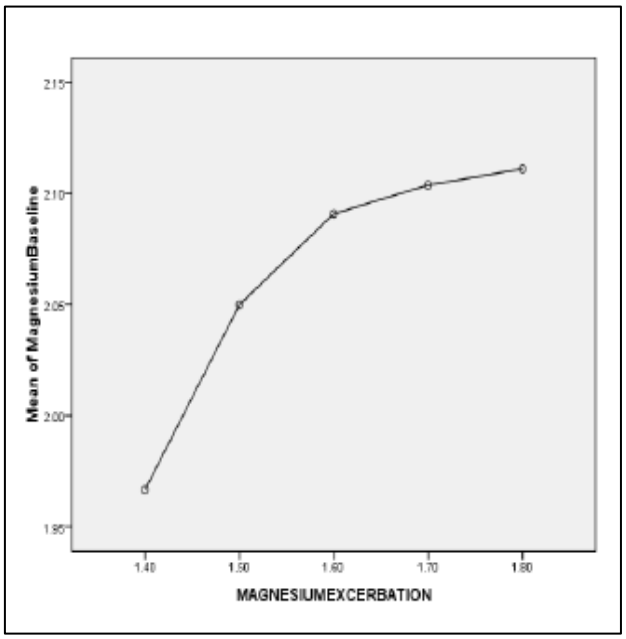

Figure 1: The serum magnesium exacerbation values are taken and the receiver operator characteristics (ROC) curve is plotted.

From the Scheffe's post hoc tests plot (Table 7 and Figure 1), the obtained mean scores of 2.11, 2.10 and 2.09 are significant from the mean score derived of 1.5 from the baseline magnesium value. So, it is concluded that the magnesium exacerbation values above the mean score of 1.6 of baseline magnesium value are significant.

A ROC curve is a graphical plot that illustrates the performance of a binary classifier system as its discrimination threshold is varied. The curve is drawn by plotting the true positive rate against the positive rate at various threshold settings. A ROC space is defined by FPR (false positive rates) and TPR (true positive rates) as x and y axes respectively, which depicts trade-offs between the true positives (benefits) and false positives. Here TPR is equivalent to sensitivity and FPR is equal to (1-specificity).

Table 2: Mean and standard deviation values of serum magnesium during stable and during exacerbation.

Variables	N	Mean	Std. dev.	Std. Error mean	P value
Magnesium baseline	100	2.0730	0.10136	0.01014	P<0.05
Magnesium exacerbation	100	1.6000	0.11459	0.01146	P<0.05

Table 3: Average values of serum magnesium for baseline and exacerbations for population sub-groups of below 60 and above 61 years old.

Groups (year)		N	Mean	Std. Dev.	T	Sig.
Below 60	Magnesium baseline	38	2.0816	0.10617	18.80	P<0.05
	Magnesium exacerbation	38	1.5816	0.12489		
Above 60	Magnesium baseline	62	2.0677	0.0988	19.20	P<0.05
	Magnesium exacerbation	62	1.6113	0.10728		

Table 4: Level of significance of magnesium baseline values based on PEFR.

Variable	PEFR	N	Mean	Std. Dev.	T	P value
Magnesium baseline	Green	96	2.0771	0.09892	2.00	P=0.048
	Yellow	4	1.9750	0.12583		

Table 5: Level of significance of magnesium exacerbation values based on PEFR.

Variable	PEFR2	N	Mean	Std. Dev	T	P value
Magnesium exacerbation	Red	96	1.6042	0.11417	1.80	P=0.075
	Yellow	4	1.5000	0.08165		

Table 6: F value of 5.62, which is greater than table value of 2.47 at 0.05 level of significance for baseline magnesium score.

Magnesium baseline					
Groups	**Sum of squares**	**Df**	**Mean square**	**F**	**Sig.**
Between groups	0.195	4	0.049	5.621	0.000
Within groups	0.822	95	0.009		
Total	1.017	99			

Table 7: Scheffe's post hoc table calculations showing increasing values of exacerbation magnesium values as compared to baseline values.

Magnesium exacerbation	N	Subset for alpha=0.05	
		1	**2**
1.4	12	1.9667	-
1.5	20	2.0500	2.0500
1.6	33	-	2.0909
1.7	26	-	2.1038
1.8	9	-	2.1111

Table 8: Depicting and confirming our findings that for sensitivity values of 0.4, the nearest corresponding magnesium values is 1.65.

Co-ordinates of the curve			
Test result variable (s)	**Positive if greater than or equal to[a]**	**Sensitivity**	**1-Specificity**
Magnesium exacerbation	0.4000	1.000	1.000
	1.4500	0.875	0.881
	1.5500	0.625	0.690
	1.6500	0.375	0.345
	1.7500	0.000	0.107
	2.8000	0.000	0.000

The test result variable(s) magnesium exacerbation has at least one tie between the positive actual state group and the negative actual state group.

The smallest cut-off value is the minimum observed test value minus 1, and the largest cut-off is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.[a]

In our study, the serum magnesium exacerbation values are taken and the ROC curve is plotted. In this graph (Figure 2), we take the measurement of the value of the line which is very close to the left upper half of the graph, as arbitrary, in the above case, the sensitivity can be taken as 0.4. These values correspond to a serum magnesium exacerbation value of 1.65. The below table also depicts and confirms our findings that for sensitivity values of 0.4, the nearest corresponding magnesium values is 1.65.

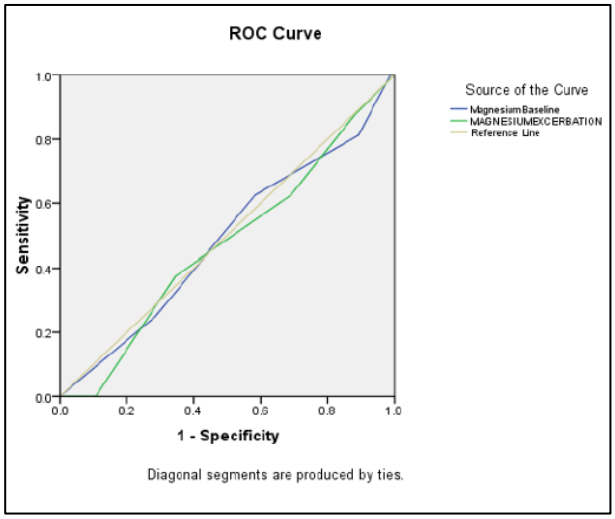

Figure 2: The ROC is plotted with magnesium exacerbation values.

DISCUSSION

Our study included 100 patients, evaluated between December 2012 and December 2013. The study consisted of 91 male patients and 9 female patients. The serum magnesium values of these patients, when they come for routine OPD visits (stable) are compared with magnesium values when they come in exacerbation, and the two results are compared.

In our study, 38 patients are aged 60 years or below and 62 of them are aged 61 years and above. This reflects that as per age wise distribution, in our study, patients above 61 years of age have a more chances to develop exacerbations of COPD.

We computed and distributed the values of serum magnesium levels during stable and exacerbation periods and results were analysed. Our stable COPD patients mean magnesium score averaged 2.08 and 2.06 mg/dl for patients below and above 60 years of age respectively. Their mean scores during exacerbation were 1.58 and 1.6 mg/dl respectively, which is significant.

Our study also concluded that that there exists a significant difference in the baseline magnesium values based on PEFR values and it was clear that patients with PEFR in the green zone have a high magnesium baseline mean score as compared to patients on yellow zone and red zone. The PEFR was measured using a peak flow meter.[14,15]

Our study also suggested a threshold level of serum magnesium of approximately 1.65 mg/dl which may be a useful therapeutic target for magnesium supplementation.

In comparison, the study done by Rajab et al also concluded that the mean serum magnesium levels of patients with acute exacerbation of COPD was statistically significantly lower 1.88±0.67 mg/dl (mean±SD) than serum magnesium of stable COPD patients 2.30±0.36 (mean±SD).[11] They also concluded that prolonged hypomagnesaemia is directly proportional to increase in number of hospital stays (days spent by the patient in the hospital).[11]

In yet another study done by Bhatt et al on 100 patients at St Luke's hospital, PA 18015, USA also concluded that hypomagnesaemia was noted in 12% percent of the patients admitted with acute exacerbations of COPD, and they also noted that serum magnesium is an independent predictor of frequent admissions.[12] Their mean score of serum magnesium during exacerbations was 1.77±0.19 mEq/l, adjusted Odds ratio 0.003 with 95% confidence intervals.[12]

Certain limitations of our study were noted. Firstly, we didn't do any therapeutic intervention (like using inhalational or intravenous magnesium sulphate). So, more evidence studies are required if earlier therapeutic interventions are essential in providing patient relief. Secondly, our follow up of patients was of a shorter duration and the number of patients we studied is of a small number. Longer follow-up and a larger sample size are required to establish a stronger correlation. Also, many of our patients were smokers, which is a common cause of COPD. So, we require a wider patient data with non-smokers also to establish a definite association between serum magnesium and exacerbations of COPD.

CONCLUSION

In conclusion, there might exist a definitive association between serum magnesium deficiency and episodes of exacerbation of COPD, although the exact mechanism behind it remains unclear. Studies requiring longer follow-up and a larger sample size would definitely help in establishing a stronger correlation, and if proved, earlier therapeutic interventions by nebulisations or injectables of

magnesium sulphate may help in immediate patient symptom relief and promising treatment strategy.

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