



ORIGINAL INVESTIGATION

Abnormalities of magnesium homeostasis in patients with chemotherapy-induced alimentary tract mucositis

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Abstract

Purpose: Hypomagnesemia contributes to morbidity in a significant proportion of hospitalized and severely ill patients, but it could also have beneficial anticancer effects. Alimentary tract mucositis is a frequent complication of cytotoxic chemotherapy. The aim of this study was to determine frequency and severity of hypomagnesemia in patients with different grades of chemotherapy-induced alimentary tract mucositis and to assess its clinical manifestations.

Methods: Multicentric observational study included 226 adult patients with alimentary mucositis treated at 3 different institutions. Patients were evaluated for severity of mucositis and the presence of hypomagnesemia, symptoms associated with hypomagnesemia, hypocalcemia, ECG changes and granulocytopenia. Subgroup analysis related to mucositis severity and presence of hypomagnesemia was performed.

Results: Patients with grade 3 or 4 alimentary mucositis expectedly had more frequent and more severe granulocytopenia than patients with milder mucositis (49.6% vs. 35.4%, $P = 0.043$), but there were no differences in rate of hypomagnesemia (24.8% vs. 26.5%). When compared to patients with normal magnesium levels, patients with hypomagnesemia had higher rates of hypocalcemia (50.0% vs. 32.7%, $P = 0.026$), QTc prolongation (15.5% vs. 3.0%, $P = 0.002$) and granulocytopenia (77.6% vs. 39.9%, $P < 0.001$), while there was no difference in symptoms or other ECG features among these subgroups.

Conclusions: Hypomagnesaemia is not associated with the severity of chemotherapy-induced mucositis. However, hypomagnesaemia was associated with higher rates of granulocytopenia and hypocalcemia. Our study failed to identify the link between hypomagnesaemia and chemotherapy-induced mucositis.

Key words: hypomagnesemia, alimentary tract mucositis, chemotherapy-induced mucositis

1. Introduction

Magnesium is the fourth most prevalent mineral in human body and the second intracellular cation just after potassium [1]. It is a key cofactor in all biochemical reactions involving adenosine triphosphate, and its depletion is often associated with other electrolyte abnormalities such as hypokalemia, hypocalcemia, and metabolic alkalosis. Hypomagnesemia occurs in more than 10% of hospitalized patients, and in up to 60% of patients in intensive care units, contributing to overall morbidity and mortality [2,3]. The most important clinical manifestations of hypomagnesemia are neurologic/neuromuscular disturbances, ECG changes and cardiac arrhythmias, changes in calcium metabolism leading to hypocalcemia and hypokalemia. Serum magnesium concentration is usually not a standard part of routine blood tests. Therefore, detection of patients with hypomagnesemia usually requires increased clinical awareness in high risk patients.

Chemotherapy-induced alimentary tract (gastrointestinal and oral) mucositis is defined as inflammatory and/or ulcerative lesions of the oral cavity and/or gastrointestinal tract induced by chemotherapeutic agents. It is an important dose-limiting side effect of chemotherapy and one of the most common causes of morbidity. It occurs in 20 - 60% of patients with solid tumors who are receiving chemotherapy [4]. Manifestations of oral mucositis include erythema, soreness and ulcers of the oral mucosa. Gastrointestinal mucositis is usually diagnosed indirectly based on the presence of diarrhea. Grade 3 - 4 oral and gastrointestinal mucositis is defined by severe symptoms interfering with oral intake of food, which occurs in 2-15% of patients [5]. Malabsorption of various nutrients, including magnesium, is one of the consequences of gastrointestinal tract inflammation and dysfunction induced by chemotherapy. However, published studies on magnesium abnormalities in patients receiving chemotherapy have been mostly focused on hypomagnesemia associated with renal wasting [6-9]. There are no studies that analyzed the impact of chemotherapy-induced mucositis on hypomagnesemia.

The aim of our study was to establish the frequency and severity of hypomagnesemia in patients with different grades of chemotherapy-induced gastrointestinal mucositis, evaluate presence of its clinical manifestations (symptoms, electrocardiogram changes, calcium

level abnormalities), and assess its relation to occurrence of other side effects of cytotoxicity.

2. Patients and methods

This multicentric observational study included 226 adult patients with symptoms of chemotherapy-induced alimentary mucositis treated at 3 different institutions in the period from September 2010 to November 2012. One hundred and thirteen patients had grade 3 or 4 alimentary mucositis and the second group consisted of 113 patients with grade 1 or 2 alimentary mucositis.

Patients had received chemotherapy for various solid malignant tumors and had received chemotherapy within 3 weeks prior to inclusion. Patients with positive bacterial culture stool test were excluded from the study. All patients have signed the informed consent, and the study was approved by local ethics committees. Grading of severity of chemotherapy side effects was made according to Common Terminology Criteria for Adverse Events, Version 4.0 [10].

Study protocol included: serum biochemistry and blood count tests, detailed medical history, physical examination and electrocardiogram. Hypomagnesaemia was defined as magnesium levels below the lower limit of normal (0.65 mmol/L).

Presence of symptoms and signs usually associated with hypomagnesemia including weakness and neuromuscular hyperexcitability was meticulously examined and noted. Electrocardiogram was analyzed for widening of the QRS complex, peaking or diminution of T waves, prolongation of the PR interval, corrected QT interval, atrial and ventricular premature systoles, and atrial fibrillation. Collected data included details on current oncologic disease and treatment, as well as history of earlier side effects and adverse events related to chemotherapy. Diagnosis and grading of chemotherapy-induced gastrointestinal mucositis was made based on examination of oral cavity, presence of diarrhea, and possibility of food intake.

2.1. Statistical analyses

Patient characteristics were assessed using descriptive statistics presented as a mean with standard deviations. Independent continuous variables were compared using Mann-Whitney test and categorical variables were compared using Fisher's exact test. Software SPSS 20.0

for Windows was used to perform all the analyses. P value <0.05 was considered significant.

3. Results

We included 226 patients with symptoms of chemotherapy-induced gastrointestinal mucositis: 113 patients with grade 1 or 2, and 113 with grade 3 or 4 alimentary mucositis. Mean age of the studied population was 63.8 ± 10.6 years, and 131/226 (58%) were females. Characteristics of the study population divided based on the severity of mucositis is presented in Table 1. There were no significant differences in demographic data between the groups. Granulocytopenia was observed in 96/226 (42.5%) of patients. Patients with grade 3/4 alimentary mucositis had higher rates and more severe

forms of granulocytopenia than patients with grade 1/2 mucositis. We found no difference in serum magnesium and calcium levels, nor the rates of hypomagnesaemia and hypocalcemia between the two groups (Table 1). In 67.9% of patients who had hypomagnesaemia, it was mild (magnesium level 0.5-0.65 mmol/L), and in the remainder it was in the range between 0.4 and 0.5 mmol/L. Fatigue and weakness were more frequently noted in patients with severe forms of alimentary mucositis (74.3% vs. 18.6%).

Study population was then divided based on the presence of hypomagnesaemia and the characteristics are presented in Table 2. Significant differences were observed in rates of granulocytopenia, hypocalcemia and QTc prolongation. Granulocytopenia was observed more frequently in patients with hypomagnesaemia.

Table 1. Anthropometric and laboratory parameters in the study population divided based on severity of alimentary tract mucositis. Continuous variables are presented as mean \pm standard deviation.

	Grade 1 or 2 alimentary mucositis (n=113)	Grade 3 or 4 alimentary mucositis (n=113)	P value
Age (years)	64.8 \pm 9.8	62.9 \pm 10.3	0.288
Gender n(%)			0.225
Male	52 (46%)	43 (38%)	
Female			
Magnesium (mmol/L) mean \pm SD	0.72 \pm 0.16	0.76 \pm 0.16	>0.3
Hypomagnesemia n(%)	30 (26.5%)	28 (24.8%)	>0.3
Leukocyte levels mean \pm SD ($\times 10^9/L$)	7.12 \pm 4.88	6.35 \pm 6.17	0.028
Granulocytopenia <2.06 $\times 10^9/L$ n(%)	40 (35.4%)	56 (49.6%)	0.043
<1.0 $\times 10^9/L$ n(%)	14 (12.4%)	33 (29.2%)	0.003
Calcium levels mean \pm SD (mmol/L)	2.25 \pm 0.16	2.12 \pm 0.21	>0.3
Hypocalcemia n(%)	39 (34.5%)	45 (39.8%)	>0.3
Fatigue/weakness n(%)	21 (18.6%)	84 (74.3%)	<0.001

Table 2. Hypomagnesemia-associated symptoms and signs in patients with low and normal magnesium levels.

	Hypomagnesemia (n=58)	Normal magnesium levels (n=168)	P value
Granulocytopenia n(%)	45 (77.6%)	67 (39.9%)	<0.001
Symptoms n(%) (fatigue/weakness)	30 (51.7%)	75 (44.6%)	>0.3
ECG changes n(%)			
Atrial fibrillation	1 (1.7%)	12 (7.1%)	0.192
PR prolongation	0	0	NA
QRS widening	7 (12.1%)	24 (14.3%)	>0.3
QTc duration >120%	9 (15.5%)	5 (3.0%)	0.002
Hypocalcemia n(%)	29 (50.0%)	55 (32.7%)	0.026

Moreover, patients with granulocytopenia had higher rates of hypomagnesemia (39.3% vs. 10.5%, $P<0.001$). Hypocalcemia and QTc prolongation was also more frequent in patients with hypomagnesemia. The presence of fatigue/weakness was similar in both groups.

4. Discussion

We found no difference in rates of hypomagnesemia, when comparing patients with mild (grade 1 or 2) and severe (grade 3 or 4) alimentary tract mucositis. This is contrary to what we have initially hypothesized. Nevertheless, hypomagnesemia was present in approximately one quarter of patients in both groups. To reach definite conclusions, rates of hypomagnesemia in our cohort of patient, should be compared with patients without any signs of alimentary mucositis. However, our study suggests that hypomagnesemia may be associated with chemotherapy-induced granulocytopenia.

As for the clinical manifestations of hypomagnesemia, in the subgroup of our patients with low magnesium levels, we have observed higher rates of hypocalcemia

and QTc prolongation, but without any difference in symptoms associated with hypomagnesaemia nor other ECG abnormalities. Absence of specific symptoms is not unusual, as most patients in our population had only mild hypomagnesemia and the symptoms usually occur only with more profound magnesium depletion [11]. Albeit fatigue or weakness was more common in patients with severe alimentary mucositis, their prevalence was similar in patients with low and normal magnesium levels. Therefore, these symptoms are probably related to other treatment-induced or disease-related morbidity.

It has been previously reported that decreased magnesium levels could have a beneficial role in terms of treatment success. This was observed in patients treated with cetuximab, which induces renal magnesium wasting [12]. These observations raise the question if hypomagnesemia should be corrected at all, in order to increase treatment efficacy [13]. Further studies are needed in order to determine the etiology and impact of hypomagnesaemia in patients with chemotherapy-induced alimentary tract mucositis.

Author contributions

NB participated in statistical analyses, reviewing the literature, writing the article and gave the final approval. FGČ gave the idea for the article, participated in data collection, drafting the article and gave the final approval. MN reviewed the previously published literature, participated in drafting the article and gave the final approval. NLj critically revised the manuscript, gave suggestions regarding data collection and analyses and gave the final approval.

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