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MAGNESIUM IN PATIENTS OPERATED DUE TO COLORECTAL OR SMALL INTESTINE CANCER AND RECEIVING TOTAL PARENTERAL NUTRITION (TPN) IN POSTOPERATIVE PERIOD

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Abstract

Magnesium is fundamental to the existence of life. The consequence of altered magnesium homeostasis may be magnesium deficiency. It is well known that magnesium plays a role in tumour biology such as carcinogenesis, angiogenesis and tumour progression. In the field of gastrointestinal cancer surgery of the clinical importance, magnesium has not been specifically studied. Therefore, the aim of our study was to evaluate changes of magnesium concentrations in patients operated due to a small intestine or colorectal cancer parenterally nurtured in comparison with a group of patients submitted to surgical interventions due to gastrointestinal cancer but receiving standard nutrition after the operation. The study group involved 78 patients operated on for gastrointestinal cancer, who were divided into 3 groups: C – patients operated due to different types of alimentary tract cancers who were provided with normal feeding after the operation, I – patients operated due to colorectal cancer who were given TPN after the operation, II – patients operated due to small intestine cancer who were given TPN after the operation. Three measurements were performed in control group (C): the 1st measurement – a day before operation, the 2nd measurement – on the third day after the operation and the 3rd measurement – on the fifth day after the operation. In the group of patients receiving TPN, three measurements were performed as well: the 1st measurement – a day before operation, the 2nd measurement – on the third day after applying TPN and the 3rd measurement – on the fifth day after applying TPN. Our studies revealed that application of TPN, conta-

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ining magnesium, in patients operated both due to colorectal cancer and small intestine cancer prevented decrease in the blood serum concentration of that element below the reference norm, which occurred in patients receiving standard diet.

Key words: magnesium, colorectal cancer, small intestine cancer, TPN.

MAGNEZ U PACJENTÓW OPEROWANYCH Z POWODU NOWOTWORU ODBYTU LUB JELITA CIENKIEGO I OTRZYMUJĄCYCH CAŁKOWITE ŻYWIENIE POZAJELITOWE (CŻP) W OKRESIE POOPERACYJNYM

Abstrakt

Magnez jest pierwiastkiem niezbędnym do życia. Konsekwencją zaburzeń homeostazy magnezu może być jego deficyt. Magnez odgrywa rolę w biologii nowotworów, tj. w karcinogenezie, angiogenezie lub rozwoju guza nowotworowego. Dotychczas nie ma szerokich badań dotyczących znaczenia magnezu w operacjach nowotworów przewodu pokarmowego. Dlatego celem badań było zbadanie zmian stężenia magnezu u pacjentów operowanych z powodu nowotworów odbytnicy lub jelita cienkiego i otrzymujących całkowite żywienie pozajelitowe w okresie pooperacyjnym, w porównaniu z grupą pacjentów poddanych interwencji chirurgicznej z powodu nowotworów przewodu pokarmowego, ale otrzymujących po operacji standardową dietę.

Badaniem objęto 78 pacjentów operowanych z powodu nowotworów przewodu pokarmowego, których podzielono na 3 grupy: kontrolną (K) – pacjenci operowani z powodu różnych nowotworów przewodu pokarmowego, po operacji otrzymujący normalne żywienie, I – pacjenci operowani z powodu zaawansowanego nowotworu odbytnicy, po operacji otrzymujący CŻP, II – pacjenci operowani z powodu nowotworu jelita cienkiego, po operacji otrzymujący CŻP. W grupie K dokonywano trzech pomiarów w kolejnych okresach: 1. pomiar – doba przed operacją, 2. pomiar – trzecia doba po operacji, 3. pomiar – piąta doba po operacji. W grupach I, II – u pacjentów otrzymujących CŻP– dokonywano również trzech pomiarów: 1. pomiar – doba przed operacją, 2. pomiar – trzecia doba po zastosowaniu CŻP, 3. pomiar – piąta doba po zastosowaniu CŻP.

W badaniach wykazano, że podawanie CŻP zawierającego magnez, zarówno chorym operowanym z powodu nowotworów odbytnicy, jak i nowotworów jelita cienkiego, zapobiega obniżeniu stężenia tego pierwiastka w osoczu krwi poniżej norm referencyjnych, tak jak to ma miejsce w przypadku pacjentów otrzymujących standardową dietę

Słowa kluczowe: magnez, nowotwór odbytnicy, nowotwór jelita cienkiego, CŻP.

INTRODUCTION

In the 1970s, nutritional treatment became commonly applied in clinical practice. It is introduced when, due to clinical or/and biochemical symptoms of malnutrition or deficiency, it is necessary to administer appropriate nutrients for supplementation. Approximately 35–50% of hospitalized patients are malnourished and in many cases the condition develops or progresses during hospitalization while surgical interventions increase the incidence of complications and prolong hospital stay (SUNGURTEKIN et al. 2004, SCHNELLDORFER, ADAMS 2005, HALL 2006, STRATTON et al. 2006). Most patients with malignant cancers suffer from malnutrition, decrease in body weight and fat-free body weight. Moreover, a decrease in body weight is the most frequent symptom of the presence of a tumour and, in over 60% of patients, development of the disease increases malnutrition. Total Parenteral Nutrition (TPN) is necessary in patients with alimentary tract cancers with metastases and stated malnutrition, who are unable to swallow or absorb food provided in a normal way for longer than 7-10 days (ECHENIQUE, CORREIA 2003). Despite numerous studies, we still lack a unanimous answer whether TPN application in patients with various tumours is beneficial or laden too many contraindications. Therefore, monitoring the malnutrition state and choosing an appropriate therapy may help to improve treatment conditions, accelerate recovery and successfully decrease costs of all medical procedures (STRATTON 2005).

Magnesium plays a crucial role in many physiological and metabolic processes. Its homeostasis is therefore fundamental to the existence of life. The consequence of altered magnesium homeostasis is magnesium deficiency. Hypomagnesaemia may cause weakness, tremors, seizures and cardiac arrhythmias (TANG, RUDE 2005). Altered plasma magnesium levels can in turn affect calcium and potassium levels (HUANG, KUO 2007, ALEXANDER et al. 2008). Moreover, magnesium plays a role in tumour biology such as carcinogenesis, angiogenesis and tumour progression (ANASTASSOPOULOU, THEOPHANIDES 2002, RUBIN 2005).

Therefore, the aim of this study has been to determine changes in blood serum magnesium concentrations in patients operated due to small intestine or colorectal cancer and parenterally nurtured in comparison with a group of patients submitted to surgical interventions due to gastrointestinal cancers but receiving standard nutrition after the operation.

MATERIAL AND METHODS

The study group involved 78 patients operated on for gastrointestinal cancer who were divided into three groups:

- C – patients operated on for different types of gastrointestinal cancer who were provided with normal feeding after the operation (on the day of an operation and during the 5 days afterwards, patients received intravenously typical amounts of liquids and essential electrolytes: *ca* 200 mmol of Na, 80 mmol of K and 300 mmol of Cl;
- I – patients operated on for colorectal cancer who were given TPN after the operation, Lublin;
- II – patients operated on for small intestine cancer who were given TPN after the operation.

The patients were chosen for the parenteral nutrition on the basis of a conducted screening examination (Table 1).

Table 1

Information about the patients

Parameter	Control (n = 20)	I (n = 34)	II (n = 24)
Sex (male/female)	14/6	22/12	18/8
Age (years ± SD)	65 ± 13.2	69 ± 10.4	58 ± 11
Body weight (kg ± SD)	58.6 ± 12.4	50.8 ± 10.6	54.3 ± 11.3
Primary tumor (n):			
Colon/rectum	7	34	
Small intestine	2		24
Esophageal	3		
Pancreas	4		
Stomach	4		

In the control group, particular measurements were conducted on the following days: 1st measurement – one day before the operation, 2nd measurement – three days after the operation, 3rd measurement – five days after the operation.

In the experimental group, three measurements were taken as well:

1st measurement – one day before the operation, 2nd measurement – three days after starting TPN, 3rd measurement- five days after starting TPN.

The patients received TPN for a period of 5 or 7 days and afterwards normal nutrition was provided.

The study was approved by the Bioethical Commission of the Medical University in Lublin (No KE-0254/31/2006).

All patients were hospitalized in the I Chair and Department of General and Transplant Surgery and Nutritional Treatment of the Medical University in Lublin, and they fully agreed to participate in the research constituting this present work.

The patients were chosen for the parenteral nutrition on the basis of a conducted screening examination. Compositions of the mixtures given in TPN are presented in Table 2.

The plasma from each blood sample was collected immediately after centrifugation at 2000 x g for 15 minutes and then stored at –20°C until analysis.

The concentration of magnesium was determined spectrophotometrically by the reaction with xylidyne blue at the wavelength 520 nm, using a Hitachi spectrophotometer. The results were expressed in mmol dm^{-3}.

Statistical analysis of the results was performed with the use of SPSS 12.0 PL software.

Table 2

Content of nutrients given in total parenteral nutrition

Group	Parameter	Mean	SD	Median	Min.	Max.	Interquartile range
I	nitrogen (g dm^{-3})	5.61	0.12	5.70	5.40	5.70	0.30
	amino acids (g dm^{-3})	38.25	3.11	40.00	33.00	40.00	7.00
	carbohydrates (g dm^{-3})	98.30	24.04	80.00	80.00	132.00	52.00
	fats (g dm^{-3})	47.60	3.76	50.00	42.00	50.00	8.00
	Na (mmol dm^{-3})	46.05	5.92	50.00	27.00	50.00	23.00
	K (mmol dm^{-3})	31.35	4.82	30.00	15.00	36.00	21.00
	Mg (mmol dm^{-3})	3.05	0.22	3.00	3.00	4.00	1.00
	Ca (mmol dm^{-3})	2.87	0.17	3.00	2.50	3.00	0.50
	Cl (mmol dm^{-3})	45.08	4.29	48.00	31.60	48.00	16.40
	Zn (mmol dm^{-3})	0.02	0.02	0.03	0.00	0.03	0.03
	acetates (mmol dm^{-3})	45.98	11.49	40.00	19.50	60.00	40.50
	phosphates (mmol dm^{-3})	11.09	5.22	7.50	5.70	18.00	12.30
II	nitrogen (g dm^{-3})	6.02	0.96	5.70	5.40	8.60	3.20
	amino acids (g dm^{-3})	39.80	7.63	40.00	33.00	60.00	27.00
	carbohydrates (g dm^{-3})	105.45	26.21	107.00	80.00	150.00	70.00
	fats (g dm^{-3})	51.05	8.85	50.00	42.00	75.00	33.00
	Na (mmol dm^{-3})	42.40	17.13	35.00	27.00	75.00	48.00
	K (mmol dm^{-3})	29.25	12.38	30.00	15.00	45.00	30.00
	Mg (mmol dm^{-3})	3.57	0.74	3.90	2.50	4.50	2.00
	Ca (mmol dm^{-3})	2.94	0.77	2.50	2.30	4.50	2.20
	Cl (mmol dm^{-3})	45.66	14.96	40.00	31.60	72.00	40.40
	Zn (mmol dm^{-3})	0.01	0.02	0.00	0.00	0.04	0.04
	acetates (mmol dm^{-3})	43.58	20.60	50.00	19.50	75.00	55.50
	hosphates (mmol dm^{-3})	11.63	6.18	11.25	5.70	23.00	17.30

The results were tested with a mixed-design variance analysis (ANOVA model). This approach, relying on the values of F test, allowed us to simultaneously analyze the influence of the group and the time of measurements on the examined parameters.

The level of statistical significance, which indicated statistically significant differences or interrelations, was $p<0.05$.

RESULTS

The magnesium concentration and values of the arithmetic mean, standard deviation (SD), median, lower and upper quartile, maximum and minimum as well as interquartile range are presented in Table 3.

Table 3

Magnesium concentration in blood serum of the three groups of patient

Group	Mg (mmol dm^{-3})	Mean	SD	Median	Lower quartile	Upper quartile	Min.	Max.	Inter-quartile range
C	Mg (1)	0.76	0.26	0.72	0.55	0.89	0.47	1.44	0.97
	Mg (2)	0.63	0.19	0.62	0.46	0.77	0.32	1.28	0.96
	Mg (3)	0.61	0.17	0.62	0.47	0.74	0.32	0.91	0.59
I	Mg (1)	0.65	0.28	0.65	0.52	0.94	0.31	0.83	0.52
	Mg (2)	0.74	0.25	0.75	0.48	0.89	0.53	1.27	0.74
	Mg (3)	0.81	0.25	0.94	0.80	1.12	0.52	1.11	0.59
II	Mg (1)	0.58	0.12	0.55	0.49	0.64	0.39	0.89	0.50
	Mg (2)	0.66	0.17	0.71	0.65	0.90	0.49	1.09	0.60
	Mg (3)	0.78	0.24	0.79	0.61	0.79	0.54	1.11	0.57

A mixed-design variance analysis according to the ANOVA model was used to test the significance of differences between subsequent measurements of magnesium concentrations. The influence of the time of measurement on magnesium concentration was checked. The analysis of variance demonstrated statistically significant differences between average values of magnesium concentrations from all the measurements (F = 12.246; $p<0.05$). The pairs of measurements that differed significantly wer 1-2 and 1-3 (post--hoc). A statistically significant decrease in the magnesium concentration between measurements 1-2 and 1-3 in the control group and a statistically significant increase in the magnesium concentration between measurements 1-3 in groups I and II were observed while comparing particular measurements (Table 4).

The influence of the affiliation to a group of patients on the magnesium concentration was also tested.

The variance analysis showed statistically significant differences between group C and groups I and II (F = 4.241 $p<0.05$). Analyses of particular groups of patients showed that on the first date of determinations, the magnesium concentration was significantly higher in group C than in group II. On the second measurement date, the Mg concentration in group I was significantly higher than in group C, and in the third date – it was significantly higher in groups receiving TPN (I and II) than in group C (Table 4).

Table 4

Statistics of significance tests of differences for particular measurements and in groups of patients

Group	Test statistics 12.246	Significance level 0.000(*)	Post-hoc 1-2, 1-3	C 1-2, 1-3	I 1-3	II 1-3
Measurement	test statistics	significance level	post-hoc	1	2	3
	4.241	0.007(*)	C-I, C-II	C-II	C-I	C-I, C-II

RESULTS AND DISCUSSION

Carcinogenesis is associated with disturbances of all metabolic processes in an organism, which results in a negative nitrogen balance, increase in glycogenesis, decrease in muscle protein synthesis and disturbances in water and electrolyte balance. There are many studies stating that hypomagnesaemia occurring in oncological patients is not only a consequence of asitia, anorexia and malnutrition but also a side-effect of drug administration and chemotherapy (ALBERDA et al. 2006). Cancer patients treated with a high dose or prolonged doses of cisplatin or cetuximab, both as monotherapy and in combination with chemotherapeutics, develop hypomagnesaemia (TEJPAR et al. 2007, VINCENZI et al. 2008).

Magnesium tolerance test, which is based on the measurement of a parenterally administered Mg load retention, is a more accurate method for the detection of Mg deficiency (RICHETTE et al. 2007), but total plasma magnesium levels measurement, as used in this study, is a standard determination method for routine diagnostic purposes. In our study, the control group consisted of patients qualified to surgical intervention due to gastrointestinal cancers, whose magnesium concentration was below the reference norm but not equal the values corresponding to hypomagnesaemia (hypomagnesaemia is defined as any decrease in the serum magnesium concentration below 0.8 mmol dm^{-3}). On the third day after an operation, the magnesium level was lower than before it and did not change on the fifth day. No symptoms of hypomagnesaemia, as cardiac arrhythmia, were observed in these patients. Numerous studies have confirmed that magnesium level decreases in patients undergoing gastrointestinal surgery (SAFAVI, HONARMAND 2007). ARMSTRONG et al. (2007) demonstrated that patients who underwent pancreaticoduodenectomy for peri-ampullary neoplasia, although generally well nourished, have lower serum micronutrient levels and a relative reduction of antioxidants versus paired controls. SCHWARZ, NEVAREZ (2005) have found in patients undergoing laparotomy, predominantly for upper gastrointestinal malignancies, that postoperative hypomagnesaemia occurred in 42% of patients without bowel preparation and in 70% of patients having bowel preparation with sodium phosphate purgative. EVANS et al. (2009), who studied statistically significant changes in the plasma magnesium in response to picolax bowel preparation and colorectal resection, observed that 34% patients became hypermagnesaemic following bowel preparation and 20% became hypomagnesaemic following resection.

In some studies, no measurements of magnesium concentration were performed after an operation, but some of the patients were observed to develop cardiac arrhythmia, which was probably caused by a decrease in the magnesium level (ATSMON, DOLEV 2005, WALSH et al. 2006). Apart of potential cases of cardiac arrhythmia, hypomagnesaemia has been implicated in the pathogenesis of prolonged postoperative ileus and pseudoobstruction (VINCENZI et al. 2008).

In our research, hypomagnesaemia before surgical intervention was observed in patients with colorectal cancer and with small intestine cancer. On the third day of TPN application, an increase in the magnesium concentration in both groups was observed. On the fifth day of the therapy, the magnesium level was within the physiological reference range. There are only a few studies monitoring magnesium levels in the postoperative period or during the postoperative nutritional therapy. In our previous study, magnesium concentration in blood serum of patients with pancreatic cancer was within the lower limits of the reference range before an operation, and the application of TPN after the operation first caused some minimal fluctuations observed on the 3^{rd} day but on the 5^{th} day, the TPN therapy brought the Mg concentration back to the same level as before the surgical intervention (SZPETNAR et al. 2009). MACHOWSKA, DUDA (2002) studied magnesium balance in patients operated due to gastric and colorectal cancer. These patients were divided into three groups: I – patients in whom postoperative magnesium concentration remained within the reference limits, II – patients in whom postoperative Mg concentration was found to be below the aforementioned reference limits for at least one day, III – patients receiving additional 2 mmol Mg^{2+} per each 500 on intravenous fluid. Magnesium concentration decreases after surgery in groups I and II were minimal, although the Mg concentration in group I remained within the reference limits, while in group II it was below them for four consecutive days. Changes in the group receiving magnesium were minimal with positive Mg balance during the first two days after surgery. PAPAGEORGIU et al. (2002) showed a significant decrease in the blood serum magnesium concentration in patients after surgery, when they were administered total parenteral nutrition. The mean value obtained during the first measurement decreased during the second and third one but rose again during the fourth measurement.

According to these studies, application of TPN containing appropriately balanced amounts of macro- and microelements may limit magnesium loss and help to improve the patients' condition after surgical intervention. This effect is ever more important as the aim of curative surgery for small intestinal carcinoma is a complete resection of the neoplasm. In carcinomas with adhesion to neighbouring organs, surgical procedure may turn into multivisceral resection. Restitution of depressed serum magnesium postoperatively may have specific benefits. Postoperative magnesium supplementation has led to a significant reduction in cardiac dysrhythmias, improved postoperative analgesia and inhibition of platelet-dependent thrombosis (SHIGA et al. 2004, SCHWARZ, NEVAREZ 2005).

Preparing appropriate TPN administrated just after the operation as well as controlling the balance of liquids and electrolytes are important steps also because of the risk of refeeding syndrome, which manifests itself by a rapid decrease in concentrations of phosphates, magnesium and potassium as well as fluid retention in the organism (HEARING 2004).

CONCLUSION

TPN is recommendable for patients with neoplastic disease and diagnosed malnutrition subjected to surgical intervention, who are unable to swallow and absorb given food for a longer period. Thus, precise and accurate calculations of the amount of administered parenteral nutrition are mandatory. Our study has revealed that application of TPN, containing magnesium, in patients operated both due to colorectal cancer and small intestine cancer prevented decrease in the blood serum concentration of this element below the physiological reference norm, which occurred in patients receiving standard diet. In patients operated due to gastrointestinal cancer, administration of parenteral nutrition is necessary even for a long time after the surgical intervention, and monitoring of the magnesium level in these patients seems to be a requisite. Determination of the efficacy of Mg supplementation if hypomagnesaemia occurs is likewise recommended.

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