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Original Research Article

Prevalence of hypomagnesemia in patients undergoing gynecological oncology surgery in tertiary care cancer institute of India

Bikram Bhardwaj*, Ava Dipan Desai, Bijal Manish Patel,
Chetna Deepal Parekh, Shilpa Mukesh Patel

Department of Gynecologic Oncology, Gujarat Cancer and Research Institute Civil Hospital Campus, Asarva Ahmedabad, Gujrat, India

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***Correspondence:**

Dr. Bikram Bhardwaj,

E-mail: bikrambhardwaj@gmail.com

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ABSTRACT

Background: Hypomagnesemia is an important but unknown risk factor for post-operative complications in patients undergoing surgery for presumed gynecological malignancy. This study aims to evaluate the prevalence of hypomagnesemia in patients undergoing surgery for presumed gynecological cancers referred to our tertiary care Cancer Institute.

Methods: This is a prospective observational study of 100 patients admitted with provisional diagnosis of malignancy. They underwent surgery in one of the Gynecologic Oncology units at The Gujarat Cancer Research Institute, Ahmedabad from October 2016 to April 2017. Hypomagnesemia was defined a serum magnesium levels less than 1.8mg/dl.

Results: The incidence of pre-operative hypomagnesemia in the entire cohort was 35%. Sixty three percent patients had normal pre-operative magnesium levels and hypermagnesemia was seen in 2% of study population. Patients with benign disease had 29.6% pre-operative hypomagnesemia compared with 39.6% in patients with gynecologic malignancy. Pre-operative hypomagnesemia and even falling levels in post-operative period are an important predictive marker for post-operative complications like increased post-operative pain, post-operative ileus, hypertension and even post-operative hypokalemia. Age, body mass index, hematocrit, surgical indication and length of hospital stay were not associated with hypomagnesemia. Patients undergoing neo-adjuvant chemotherapy before surgery had significant incidence of hypomagnesemia both pre-operatively and post-operatively.

Conclusions: Hypomagnesemia is quite prevalent in patients of gynecologic-oncology undergoing surgery. Pre-operative hypomagnesemia and even falling levels in post-operative period have a bearing on the final surgical outcome. Hence pre-operative and post-operative magnesium levels may be included as a valuable marker in all patients undergoing surgery for gynecologic malignancy.

Keywords: Gynec-oncology surgery, Hypomagnesemia, Hypokalemia, Post-operative complications

INTRODUCTION

Magnesium is the second most abundant element inside human cells and the fourth most abundant positively charged ion in the human body. Magnesium is crucial to

more than 300 enzyme driven biochemical reactions in the body on a near constant basis.¹

Magnesium is one of the most common co-factors in the body. Its presence is crucial to

- Glucose and fat breakdown
- DNA and RNA synthesis
- Regulation of cholesterol synthesis
- Production of proteins and enzymes and
- anti-oxidants like glutathione

Without magnesium we could not produce energy and our muscles would go into a permanent state of contraction. It also plays a pivotal role in the reactions that generate and use ATP, the fundamental unit of energy within the cells of the body. Magnesium is a macro-mineral which unlike trace minerals is required by the body in large amounts. The average human body contains 25 grams of magnesium, one of the six essential elements which must be supplied in diet.

Hypomagnesemia is an electrolyte disturbance in which there is low level of magnesium in the blood. Normal magnesium levels are between 1.8-2.5 mg/dl, with levels less than 1.8 mg/dl defining hypomagnesemia. Magnesium deficiency is not uncommon in hospitalized patients. Twelve percent of admitted cancer patients and as high as 60-65% of patients in intensive care units have hypomagnesemia.²⁻⁴ Thirty percent alcoholics and 25% diabetic patients have hypomagnesemia. Hypomagnesemia is probably under-diagnosed as testing for serum magnesium levels is not done routinely. Symptomatic hypomagnesemia is commonly associated with hypokalemia, hypocalcemia and metabolic alkalosis. Correction of hypokalemia is challenging without correcting hypomagnesemia.⁵ A number of medical conditions and interventions associated with hypomagnesemia include^{8,9}

- Major surgery requiring bowel preparation with sodium phosphate enema.
- Chemotherapy especially platinum compounds
- Diabetes and obesity
- Drugs like diuretics, gentamycin, digitalis, cyclosporine and long term use of proton pump inhibitors
- Trauma, infection, sepsis Transfusion of blood products preserved with citrate
- Alcoholism, starvation and malnutrition.

Malnutrition occurs upto 20% in gynecologic oncology patients with maximum incidence in ovarian cancers. Patients undergoing surgery for gynecological cancer undergo a number of interventions and have associated medical conditions which cause hypomagnesemia. Hence, the present study aims to evaluate the prevalence and risk factors associated with hypomagnesemia in patients under-going surgery for gynecological malignancy.

METHODS

This is a prospective study of 100 patients who underwent surgery in one of the Gynaecologic- Oncology

unit of The Gujarat Cancer and Research Institute, Ahmedabad for suspicion of malignancy. The present study aims to evaluate the prevalence and risk factors for hypomagnesemia in patients undergoing surgery for gynecological malignancy between October 2016 to April 2017.

Inclusion criteria

All patients undergoing major surgery for suspicion of gynecological malignancy from October 2016 to April 2017. Major surgery included abdominal hysterectomy, exploratory laparotomy, radical hysterectomy, radical vulvectomy and tumor de-bulking.

Exclusion criteria

All patients with gynecological malignancy during same time period undergoing other treatment modalities like radiotherapy and chemotherapy. Patients given sodium phosphate enema for bowel preparation were also excluded from the study. Patients undergoing minor surgery during same time period were excluded from the study.

Patients were reviewed for age, BMI, surgical indication, type of surgery, pre-operative and post-operative laboratory values, pre-operative and postoperative pain and medical history of diabetes and hypertension. Patients were included in analysis as having malignancy whether diagnosed pre-operatively or post-operatively. Sodium phosphate enema was not used for bowel preparation in any of the cases.

Pre-operative and post-operative sodium, potassium, calcium and magnesium were assessed. Pre-operative laboratory analysis occurred within 2 weeks of surgery and post operative analysis was done on day1. Sodium (135-145 meq/L), potassium (3.5-5.2meq/L), calcium (9-10.2 mg/dl) and magnesium (1.8-2.5 mg/dl) were considered normal. The incidence of pre-operative and post-operative hypomagnesemia was assessed. Pain scores were graded from 0 to 10 using Universal Pain Assessment Tool.

Pre-operative pain assessment was done on the day of admission for surgery and post-operative pain scores were obtained during morning rounds on day 1 of surgery. All patients underwent combined epidural and general anaesthesia and received post-operative fluid resuscitation with lactated Ringers solution. Post-operative electrolyte deficiencies were corrected intravenously on day1. Age, BMI, medical history, surgery type, length of stay and post-operative pain scores were assessed for association with hypomagnesemia. Due to very less incidence of hypermagnesemia and aim to assess the impact of hypomagnesemia patients with normal magnesium levels and hypermagnesemia were combined to analyse the risk factors.

Statistical analysis

For demographic data comparing 3 groups according to magnesium values, analysis of variance was used for continuous variables and X² or Fischer exact test was used for categorical variables. For other data to compare hypomagnesemia to normal and hypermagnesemia combined, t test was used for continuous variables and X² or Fischer exact test was used for categorical variables.

RESULTS

One hundred patients were enrolled for surgery with suspicion of malignancy from October 2016 to April 2017. Mean age of the study population under study was 49.5 years (range 15-76 years).

Ninety patients were vegetarians (90%). Nine patients (9%) had history of infertility and five patients were unmarried. Sixty patients were postmenopausal and 40 patients were premenopausal.

Mean BMI of the study population was 22.2 (Range 17-32). Co-morbidities in the form of diabetes, hypertension, hypothyroidism and coronary artery disease were present in 14, 26, 4 and 3 patients respectively in the study population. Thirty patients were subjected to neo-adjuvant chemotherapy before undergoing surgery for gynecological malignancy. Out of 100 patients, final histology was malignant in 69 cases, 25 cases had benign histology and remaining 6 cases had pseudo-tumors.

Table 1: Clinical profile of women undergoing surgery for provisional diagnosis of gynecological malignancy (n=100).

Variable	Number (%)
Age-median (range) yrs	49.5 (15-76) years
Menstrual status	
Premenopausal	40 (40%)
Postmenopausal	60 (60%)
Vegeterians	90 (90%)
Mean BMI	22.2 (15-76) Kg/m ²
Co-morbidities	
Diabetes	26 (26%)
Hypertension	14 (14%)
Hypothyroidism	4 (4%)
Coronary artery disease	4 (4%)
Pre-operative Magnesium	
<1.8mg/dl	35 (35%)
>1.8mg/dl	65 (65%)
Post-operative Magnesium	
<1.8mg/dl	64 (64%)
>1.8mg/dl	36 (36%)
Neo-adjuvant chemotherapy	30 (30%)

The prevalence of hypomagnesemia among the study population undergoing gynecologic surgery was 35% pre-operatively (p<0.001) and 64% post-operatively (p<0.001). Among patients with benign disease 29.6% had pre-operative hypomagnesemia compared with 39.6% of patients with gynecological malignancy.

Table 2: Patient demographics.

Variable	Hypomagnesemia	Normal	Hypermagnesemia	Total	P value
All patients (pre-operative)	35	63	02	100	<0.0001
All patients (post-operative)	65	34	01	100	<0.0001
Mean Age (years)	51years	49years	53.5years	52	0.98
Average BMI (Kg/m ²)	23.1	25.1	22.5	24.4	0.93
Malignancy					
Yes	51	17	01	69	0.012
No	13	17	01	31	
Total	64	34	02	100	
Cancer type					
Uterine	02	02	0	04	0.85
Cervical	04	03	0	07	
Ovarian	38	21	01	60	
Vulvar	04	06	0	10	
Endometrium	10	08	01	19	
Uterine	02	02	0	04	
Total	58	40	02	100	

The median age was 51 years for patients with pre-operative hypomagnesemia and 49 years for patients with normal pre-operative magnesium levels (P=0.98). The

median BMI for patients with hypomagnesemia before surgery was 23.1Kg/m² and 25.1Kg/m² for patients with normal pre-operative magnesium levels (P=0.93).

Table 3: Variables for pre-operative hypomagneseemia.

	Mg<1.8mg/dl	Mg>1.8mg/dl	Total	P value
Cancer Type				
Ovarian cancer	21 (35%)	39 (65%)	60	0.776
Cervical cancer	03 (42.8%)	04 (57.2%)	07	
Uterine cancer	01 (25%)	03 (75%)	04	
Endometrial cancer	08 (42.1%)	11 (57.9%)	19	
Vulvar cancer	02 (20%)	08 (80%)	10	
Co-morbidities				
Hypertension				
Yes	09 (25.7%)	13 (20%)	22	0.68
No	26 (74.3%)	52 (80%)	78	
Total	35	65	100	
Diabetes				
Yes	07 (20%)	08 (12.3%)	15	0.46
No	28 (80%)	57 (87.7%)	85	
Both DM, HTN				
Yes	05 (14.2%)	01 (1.5%)	06	0.055
No	30 (85.8%)	64 (98.5%)	94	
Potassium				
<3.6mg/dl	06 (17.1%)	04 (6.1%)	10	0.018
3.6-5.2mg/dl	28 (80%)	60 (92.3%)	88	
>5.2mg/dl	01 (2.9%)	01 (1.6%)	02	
Total	35	65	100	

Table 4: Variables for post-operative hypomagneseemia.

Cancer type	Mg<1.8mg/dl	Mg>1.8mg/dl	Total	P value
Ovarian cancer	39	21	60	0.432
Cervical cancer	05	02	07	
Uterine cancer	02	02	04	
Endometrial cancer	14	05	19	
Vulvar cancer	04	06	10	
Co-morbidities				
Hypertension				
Yes	17 (26.5%)	05 (13.8%)	22	0.20
No	47 (73.5%)	31 (86.2%)	78	
Total	64	36	100	
Diabetes				
Yes	10 (15.6%)	04 (11.1%)	14	0.048
No	54 (84.3%)	32 (88.9%)	86	
Total	64	36	100	
Both DM, HTN				
Yes	05	01	06	0.414
No	59	35	94	
Total	64	36	100	
Lab data Hematocrit				
27-31	54	32	86	0.76
31.1-35	10	04	14	
Total	64	36	100	
Potassium				
<3.6mg/dl	23	06	29	0.047
3.6-5.2mg/dl	39	30	69	
>5.2mg/dl	02	0	02	
Total	64	36	100	

Malignancy was associated with pre-operative and post-operative hypomagnesemia (P=0.012). However, cancer type was not indicative of hypomagnesemia among patients with malignancy before surgery (P=0.776).

Hypertension alone was not associated with pre-operative hypomagnesemia (P=0.68) whereas it was associated with hypomagnesemia if patients also had diabetes (P=0.019).

Table 5: Effect of neo-adjuvant chemotherapy (NACT) on magnesium levels.

Pre-operative Mg>1.8mg/dl	Post-operative Mg<1.8mg/dl	Post-operative Mg>1.8mg/dl	Total	P value
15	21	09	100	0.04
50	43	27	100	

Diabetes alone was not associated with pre-operative hypomagnesemia (P=0.46). Surgical indication and classification were not associated with pre-operative hypomagnesemia (P=0.776)

Pre-operative hematocrit levels had no association with pre-operative hypomagnesemia (P=0.055). Thirty patients in our study were exposed to neo-adjuvant chemotherapy before undergoing surgery. 15 (50%) had pre-operative magnesium levels less than 1.8mg/dl whereas 21 (70%) had post-operative hypomagnesemia.

Table 6: Peri-operative outcome associated with hypomagnesemia- post-operative.

Variable	Mg<1.8mg/dl	Mg>1.8mg/dl	P value
Average length of stay	7.6	6.25	0.60
Pain score	3.4	2.4	0.049

Post-operative hypomagnesemia had a strong association with major surgery, exposure to chemotherapy (P=0.04), diabetes (P=0.048) and hypokalemia (P=0.047). Surgical indication was not associated with post-operative hypomagnesemia (P=0.432). There was no direct association of post-operative hypomagnesemia with hypertension (P=0.20) and post-operative haematocrit (P=.41). Diabetes had a significant association with post-operative hypomagnesemia (P=0.048).

Hypomagnesemia had an association with pre-operative and post-operative pain (P=0.048) but not with average length of stay (P=0.60). However, very low levels of magnesium less than 1 mg/dl had a strong association with prolonged intensive care unit stay and even requirement of ventilatory support adding to the length of stay in the hospital. Thirteen patients in our study had post-operative ileus. Of these 11 patients had hypomagnesemia.

Five patients had new onset hypertension with associated hypomagnesemia in 4 cases. Aggravation of pre-existing hypertension is seen in 10 cases with associated

hypomagnesemia in 8 of them. Five patients were admitted in intensive care unit requiring ventilator support. Of these 4 patients had critically low magnesium levels.

Table 7: Prevalence of hypomagnesemia according to tumor type.

Tumor type (Total)	Mg<1.8mg/dl	Mg>1.8mg/dl
Malignant (69)	51 (73.9%)	18 (26.1%)
Benign (25)	09 (36%)	16 (64%)
Pseudo-tumor (6)	04 (66.6%)	02 (33.4%)

Malignant tumors

Out of total 100 patients, 69 patients had final malignant histology. Fifty one patients with malignant histology had post-operative hypomagnesemia. Major post-operative complications in the form of post-operative ileus occurred in 10 patients.

Ten patients had new onset hypertension detected intra-operatively requiring anti-hypertensive intra-operatively and in the immediate post-operative period and 5 patients had aggravation of pre-existing hypertension.

Three patients with magnesium levels less than 1mg/dl had admissions in intensive care unit. Three patients with levels less than 1mg/dl had convulsions.

Benign tumors

Out of total 100 cases, 25 patients had final benign histology. Hypomagnesemia was present in 9 patients. Two patients had post-operative ileus and 1 patient had very low magnesium levels and was admitted in ICU with aggravation of pre-existing coronary artery disease requiring ventilatory support.

Pseudo-tumors

There were 6 cases of pseudo-tumors in our study. Hypomagnesemia was present in 4 of them. 1 patient had post-operative ileus and 1 patient had aggravation of pre-existing hypertension.

Table 8: Common post-operative complications and their incidence according to tumor type.

Complications (No.)	Malignant	Benign	Pseudo-tumor	Mg <1.8mg/dl
Ileus (13)	10	02	01	11
New onset HTN (5)	03	02	0	04
Aggravation of HTN (10)	07	02	01	08
Convulsions (3)	03	0	0	03
ICU admission and ventilatory support (5)	03	01	01	04

DISCUSSION

Magnesium is a mineral utilized by each organ as a part of our body, particularly heart muscles and kidneys. The total body stores of magnesium are between 21 and 28 grams in an average 70 kg man. Normal magnesium levels are 1.8 to 2.5mg/dl. Most of the magnesium level in the body is in the skeletal bony mass which accounts for more than 50% of the body stores. The root-cause behind the ill effects of unexplained exhaustion, strange heart rhythms or even muscle fits and eye jerks lies in the low magnesium levels. Early signs of magnesium deficiency include loss of appetite, headache, nausea, fatigue and weakness. Serious manifestations of hypomagnesemia include seizures, coronary spasms, abnormal heart rhythms and personality changes. A study published in the American Journal of Clinical Nutrition revealed that higher intake of dietary magnesium was connected with lower risk of colorectal tumors. Vegetables like spinach, beans, nuts, seeds, avocados, pumpkin and sunflower are rich sources of magnesium. About 30-40% of dietary magnesium is absorbed principally in jejunum and ileum and is stimulated by Vitamin D.

Hypomagnesemia has been linked to poor outcome in several different patient populations. In a study of nearly 21000 patients on maintenance dialysis, patients with lowest magnesium levels were at highest risk for death. Hypomagnesemia is a common development in critically ill sepsis patients and indicates poor prognosis. There is a significant association between hypomagnesemia and increased need for mechanical ventilation, prolonged intensive care unit stays and increased mortality in this subset of population based on observational studies. In a Mayo Clinic review of 65,974 hospitalised adult patients hypomagnesemia on admission was associated with increased hospital mortality. Death rates were 2.2% in patients with magnesium levels of 1.5-1.69mg/dl and 2.4% in those with levels below 1.5mg/dl as compared to 1.8% in patients with levels of 1.7-1.89 mg/dl. The present study reveals hypomagnesemia is prevalent both pre-operatively(35%) and post-operatively(64%) in a significant proportion of patients undergoing surgery for gynecological cancer.^{4,10,11} Even falling levels of serum magnesium in post-operative period has a bearing on the final surgical outcome. Falling serum magnesium levels indicate the magnitude of surgical stress which has a positive impact on post-operative complications.

Prevalence of hypomagnesemia is more after surgery similar to other studies evaluating serum magnesium in post-operative period.² In present study the prevalence of post-operative hypomagnesemia was 64%. Hypomagnesemia was associated with major surgery especially abdominal surgery in patients cared for by surgical oncologists.^{7,9,12} Schwartz et al demonstrated significant decreases in potassium, calcium, and phosphate along with hypomagnesemia in patients after laparotomy.¹² In present study hypomagnesemia was associated with hypokalemia in 23% and hypocalcemia in 64% cases respectively in post-operative period. Schwarz et al also found that hypomagnesemia did not increase length of hospital stay, although other studies concluded a longer length of stay in critically ill patients with hypomagnesemia.^{13,14} In present study the average length of stay in patients with post-operative hypomagnesemia was 7.6 days which was in comparison with patients having normal magnesium levels (6.25 days).

The significantly higher preoperative and postoperative pain scores that we report in patients with a low magnesium level correlate to previous research on the potential analgesic benefit of magnesium, although this theory is represented by conflicting results in the literature. Tramer et al found that patients had less post-operative analgesic requirement and experienced a better quality of sleep when given peri-operative magnesium sulfate. This effect has, however, not been universally replicated or recognized. In present study, there was a significant increase of pain score to 3.4 in patients with hypomagnesemia compared to 2.4 in patients with normal magnesium levels. In a systematic review, Lysakowski et al found that 4 studies concluded a significant fall in pain killer requirements and pain intensity with peri-operative magnesium supplementation, whereas 4 other studies showed no such difference in either outcome.¹⁵ The effect of postoperative magnesium repletion has been evaluated and is, however, likely that serum magnesium is an identifiable marker of a more complex underlying problem resulting in decreased pain tolerance.

Consequences of hypomagnesemia can range from mild to severe. Electrolyte imbalances associated with hypomagnesemia include hypokalemia, hypocalcemia, hypoalbuminemia, and hypophosphatemia.^{4,5,12,16} In present study there was associated hypokalemia (23%) and hypocalcemia (64%) along with hypomagnesemia (64%) in post-operative period. Severe hypomagnesemia

(<1.0 mEq/dL) in intensive care patients is associated with a higher mortality rate, need for ventilatory support, and prolonged duration of mechanical ventilation.^{5,16} In current study 3 patients had magnesium levels less than 1mg/dl. Two of these patients had convulsions and 1 patient had ECG abnormality in the form of atrial fibrillations. All 3 patients were admitted in intensive care unit and required ventilatory support. Severe hypomagnesemia has also been associated with torsades de pointes.¹⁸ Magnesium deficiency has also been postulated to play a role in the development of myocardial infarction.¹⁹ One study even suggests that routine serum magnesium levels may identify patients at risk for myocardial infarction.²⁰ In present study none of the patients with hypomagnesemia had myocardial infarction. However, 2 patients in present study with severe hypomagnesemia had cardiac decompensation in the form of atrial fibrillations and acute left ventricular failure respectively.

Hypokalemia is a common event in patients with hypomagnesemia, occurring in 40 to 60% of cases. In present study, the incidence of hypokalemia with associated hypomagnesemia was 23%. This is partly due to underlying disorders that cause magnesium and potassium losses including diuretic therapy and diarrhea. The earliest manifestation of hypomagnesemia include neuromuscular irritability in the form of tetany, Chvosteks and Trousseau's signs and convulsions. The threshold of axon stimulation is decreased and nerve conduction velocity is increased when serum magnesium is reduced, leading to an increase in excitability of muscles and nerves. Two patients with very low magnesium levels in post-operative period had convulsions.

Hypomagnesemia is now a recognized cause of cardiac arrhythmias. ECG changes include prolongation of conduction and non specific ST depression. Patients with hypomagnesemia are particularly susceptible to digoxin related arrhythmias. One patient in our study had atrial fibrillations. The incidence of cardiac arrhythmias also correlate with degree of magnesium deficiency in patients with coronary artery disease. Very low magnesium levels can cause torsades de pointes.¹⁸ Magnesium supplementation may reduce the frequency of potentially fatal ventricular arrhythmias. It has been suggested that magnesium plays a role in blood pressure regulation. Hypertension appears to be uniformly characterized by a decrease in intracellular free magnesium that, due to increased vascular tone and reactivity causes an increase in total peripheral resistance. Magnesium deficiency is also known to be accompanied by thrombotic tendencies, increased platelet aggregation and increased coronary artery responsiveness to contractile stimuli. These factors are important in initiation of acute myocardial infarction.¹⁹ Research is conflicting regarding the benefits of intravenous administration of magnesium in the setting of acute myocardial infarction. In present study, we had 10 cases where there was aggravation of pre-existing

hypertension associated with hypomagnesemia in post-operative period requiring further dose adjustments of anti-hypertensives. Five cases had new onset hypertension associated with hypomagnesemia requiring some anti-hypertensive treatment intra-operatively and in the immediate post-operative period. Hypomagnesemia has a lot of bearing on the post-operative outcome. Post-operative ileus is one of the major complications in the immediate post-operative period associated with hypomagnesemia. In our study 13 patients had post-operative ileus. Eleven of these patients had hypomagnesemia and 8 patients had concomitant hypomagnesemia along with hypokalemia.

Main limitation of this study is the small size of study population. Another limiting factor is not stratifying surgical procedures into routine and complex surgeries. More intensive cases such as debulking procedures and bowel anastomosis including confounding factors such as prolonged operative time, peri-operative morbidity and blood loss were not taken into account in this study

CONCLUSION

Hypomagnesemia is a lesser known risk factor for post-operative complications in patients with gynecological malignancies. The present study reveals hypomagnesemia is prevalent both pre-operatively and post-operatively in a significant proportion of patients undergoing surgery with suspicion of gynecological malignancy. Even falling levels of serum magnesium in post-operative period have a bearing on the final surgical outcome. Female patients undergoing gynecological surgery are more prone to electrolyte imbalance because of associated co-morbid conditions like diabetes and hypertension and use of certain medications like diuretics and proton pump inhibitors by these patients. Serum magnesium is a relatively low cost test which should be utilized more frequently as a prognostic tool to reduce the risk of adverse surgical outcomes. The impact of pre-operative nutrition in patients suffering hypomagnesemia and its impact on post-operative outcome as well as prognosis in patients undergoing surgery for gynecological cancers needs to be further elucidated.

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