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Araştırma

Postoperative hypomagnesemia incidence in patients with epithelial ovarian cancer after hyperthermic intraperitoneal chemotherapy

İntraperitoneal hipertermik kemoterapi alan epitelyal yumurtalık kanseri olan hastalarda postoperatif dönemde hipomagnezemi insidansı

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ABSTRACT

Objective: Hyperthermic intraperitoneal chemotherapy (HIPEC) is an emerging treatment modality for patients with epithelial ovarian cancer (EOC) following maximal cytoreductive surgery (CRS). This study aims to evaluate the development of hypomagnesemia without elevated serum creatinine levels in patients with EOC who underwent CRS-HIPEC.

Materials and Methods: It was a retrospective study analyzing the patients (n=43) with advanced stage EOC undergoing HIPEC following the CRS at two tertiary hospitals in Istanbul between September 2014 and August 2018.

Results: A total of 43 patients with EOC were enrolled in this retrospective study. Eight of them developed hypomagnesemia. The incidence of hypomagnesemia was found as 18.6% in this study. The mean onset time of hypomagnesemia was three days (range, 1-6 days). Hypomagnesemia developed in five of 32 patients (15.6%) treated with cisplatin, two of 10 patients (20.0%) treated with carboplatin, and one patient treated with mitomycin C. None of the patients had a neurological symptom.

Conclusion: Multiple morbidities, including hypomagnesemia, must be considered in the management of patients with EOC undergoing CRS-HIPEC. Hypomagnesemia is a potential complication associated with CRS-HIPEC, and it cannot be predicted preoperatively. The results of this study suggest routine measurement of magnesium levels in the preoperative and postoperative period in order to rule out hypomagnesemia and when found its early management.

Keywords: Ovarian cancer, HIPEC, cisplatin, hypomagnesemia, nephrotoxicity

ÖZET

Amaç: İntraperitoneal hipertermik kemoterapi (HİPEK), maksimal sitoredüktif cerrahiyi (SC) takiben epitelyal yumurtalık kanseri (EYK) olan hastalar için ortaya çıkan bir tedavi yöntemidir. Bu çalışma, SC-HİPEK uygulanan EYK hastalarında yüksek serum kreatinin düzeyleri olmadan hipomagnezemi gelişimini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Eylül 2014-Ağustos 2018 tarihleri arasında İstanbul'daki iki üçüncü basamak hastanede SC sonrası HIPEC uygulanan ileri evre EYK hastalarını (n = 43) inceleyen retrospektif bir çalışmadır.

Bulgular: Bu retrospektif çalışmaya toplam 43 EYK hastası dahil edildi. Bunlardan sekizinde hipomagnezemi gelişti. Bu çalışmada hipomagnezemi insidansı %18,6 olarak bulundu. Ortalama hipomagnezemi başlangıç süresi üç gündü (aralık, 1-6 gün). Sisplatin ile tedavi edilen 32 hastanın beşinde (%15,6), karboplatin ile tedavi edilen 10 hastanın ikisinde (%20,0) ve mitomisin C ile tedavi edilen bir hastada hipomagnezemi gelişti. Hiçbir hastada nörolojik bir semptom saptanmadı.

Sonuç: SC-HİPEK uygulanacak EOC hastalarının tedavisinde hipomagnezemi dahil çoklu morbiditeler düşünülmelidir. Hipomagnezemi, SC-HİPEK ile ilişkili potansiyel bir komplikasyondur ve ameliyat öncesi tahmin edilemez. Bu çalışmanın sonuçları hipomagnezemiyi ekarte etmek ve erken tedavisini saptamak için ameliyat öncesi ve sonrası dönemde magnezyum düzeylerinin rutin olarak ölçülmesini önermektedir.

Anahtar Kelimeler: Yumurtalık kanseri, HİPEK, sisplatin, hipomagnezemi, nefrotoksisite

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Introduction

Ovarian cancer is the second most common gynecological cancer in developed countries, and the fifth most common cause of cancer-related death in women (1). The majority of the patients with ovarian cancer is diagnosed at the advanced stages. Standard of care for the patients with epithelial ovarian cancer (EOC) includes maximal cytoreductive surgery (CRS) defined as no residual disease followed by six cycles of chemotherapy, including carboplatin and paclitaxel with or without targeted therapy. However, if the patient is inoperable, first neoadjuvant chemotherapy is started.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is an emerging treatment modality for the intraperitoneal carcinomatosis and exerts its effect via a chemotherapeutic agent of which activity is enhanced by the hyperthermia. The most commonly used agent is cisplatin. CRS, together with HIPEC, has been showed to increase the overall survival rate in patients with advanced-stage EOC in a multi-center randomized study (2). Nevertheless, it is not involved in the gold standard treatment of EOC. Commonly reported complications with HIPEC include nephrotoxicity. There are several studies reported acute kidney injury (AKI) postoperatively due to HIPEC (3-5). Additionally, different electrolyte disorders, including hypomagnesemia, hypopotassemia, and hyponatremia, may occur following the HIPEC (6). Patients with uncorrected magnesium deficiency may develop neurologic deterioration, and effective magnesium therapy is necessary. Hakeam et al. reported an incidence of hypomagnesemia as 30% following the CRS-HIPEC with cisplatin and doxorubicin in the patients with gynecological cancer (4).

This study aims to evaluate the development of hypomagnesemia without elevated serum creatinine levels in patients with EOC who underwent CRS-HIPEC. We propose monitoring of electrolytes, including magnesium levels after HIPEC, in order to determine hypomagnesemia. Thus, we hope to detect the specific drug-related morbidity and improve the perioperative management of patients undergoing CRS and HIPEC.

Materials and Methods

Patient population

The patients with advanced ovarian cancer undergoing HIPEC following the CRS at the Department of Obstetrics and Gynaecology in Koc University Hospital and American Hospital between September 2014 and August 2018 were included in the study. Patients with a failure to obtain informed consent, a history of acute renal injury, low estimated glomerular filtration rate (eGFR), and non-epithelial ovarian cancer were not included. All CRSs were performed by the co-author experienced gynecologic oncology surgeons (D.V., M.A., and C.T.). Patients were informed before surgery, and signed written consent was taken for possible risks. All patients received antibiotic prophylaxis and low-molecular-weight heparin. Serum electrolytes were measured daily as a part of routine practice.

The current study was approved by the Koc University Institutional Review Board (approval number: 2018.166.IRB2.030).

Data collection

Only the patients who received postoperative magnesium therapy following CRS-HIPEC due to hypomagnesemia were included in the study. Hypomagnesemia, hypopotassemia, and hyponatremia were defined as a serum level of less than 1.7 mg/dl, 3.5 mmol/L, and 135 mmol/L, respectively. Baseline clinicopathological variables, intraoperative data, and pre-, intra-, and postoperative laboratory results were evaluated. The baseline characteristics including age, body mass index, comorbidities; and preoperative laboratory tests consisting complete blood count (CBC), serum albumin, serum potassium, serum creatinine, and blood urea nitrogen (BUN); and surgical data comprising volume of ascites, the chemotherapeutic agent used for HIPEC, erythrocyte suspension (ES) and/or fresh frozen plasma (FFP) transfusion(s), volume of crystalloid and/or colloid given, albumin replacement, and arterial blood gas (ABG) at the beginning, before, and after HIPEC were recorded.

Maximal cytoreductive surgery and HIPEC procedure

All procedures were performed under general anesthesia in the dorso-lithotomy position. Total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), bilateral pelvic-paraaortic lymphadenectomy (BPPALND), omentectomy (OMM), and appendectomy (APP) were performed as the standard surgical approach in all newly diagnosed patients. Cytoreductive surgery including diaphragmatic stripping, liver metastasectomy, recto-sigmoidectomy, ileum resection, celiac lymphadenectomy, cholecystectomy, peritonectomy, distal pancreatectomy, splenectomy, colectomy, subtotal gastrectomy, omentectomy, ureter excision, partial bladder excision, cardio-phrenic lymphadenectomy, resection of pancreatic capsule with posterior duodenal wall, and metastasectomy of abdominal wall were performed if needed. Two inflow catheters and

two outflow catheters were placed at the end of the CRS. The closed abdomen technique was performed, after the abdominal fascia and skin were closed with a running suture. The abdominal cavity was filled with a peritoneal dialysis solution, then perfused at a temperature of 410C to 420C for 15 minutes. The intraabdominal temperature was measured at the inflow catheter and the outflow catheters. One of the three different chemotherapeutic agents (cisplatin 75 mg/m^2, carboplatin 800 mg/m^2, or mitomycin C 20 mg/m^2) was administered and circulated continuously for 60 minutes with the use of a roller pump through a heat exchanger. In order to maintain the urine output of 50 to 100 ml/hour in all cases during HIPEC, a fluid load was administered near the end of CRS and before HIPEC.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) Version 24.0 for Mac Os X (Chicago, IL, USA) was used to both enter and analyze the data. Median, mean, standard deviation, frequency, and ratio values were used for descriptive statistics.

Results

A total of 43 patients with ovarian cancer were enrolled in this retrospective study. Eight of them met the inclusion criteria. The median age was 53 years (range, 47-68 years). The demographic and clinical characteristics of patients with EOC who underwent CRS-HIPEC, followed by hypomagnesemia, are shown in Table 1. Five of these eight patients were newly diagnosed with high-grade serous ovarian cancer, and three patients had recurrent high-grade serous ovarian cancer. Four of five newly diagnosed patients had received neoadjuvant chemotherapy with carboplatin and paclitaxel before the interval CRS-HIPEC. TAH, BSO, BPPALND, OMM, and APP were performed as the standard surgical approach in five newly diagnosed patients. In addition, recto-sigmoidectomy was performed in 1 patient; ileum resection was performed in 2 patients; liver metastasectomy was performed in 4 patients; celiac lymphadenectomy was performed in 1 patient; colon resection was performed in 4 patients; cholecystectomy was performed in 2 patients; peritonectomy was performed in 4 patients; diaphragmatic stripping was performed in 4 patients; distal pancreatectomy was performed in 2 patients; splenectomy was performed in 3 patients; and subtotal gastrectomy was performed in 1 patient. Three patients had recurrent high-grade serous ovarian cancer. One of the recurrent patients previously received CRS-HIPEC five years ago. Gastric antrum resection, BPPALND, OMM, liver metastasectomy, and APP were performed in one patient; colectomy, cholecystectomy, diaphragmatic stripping, peritonectomy, left ureter excision, partial bladder excision, liver metastasectomy, and splenectomy were performed in the second patient; cholecystectomy, cardio-phrenic lymphadenectomy, resection of pancreatic capsule with posterior duodenal wall, and metastasectomy of abdominal wall were performed in the third patient. Maximal CRS was achieved in all patients. The surgical procedures performed during CRS are shown in Table 3. After CRS, one of the three chemotherapeutic agents, including cisplatin, carboplatin, or mitomycin C was administered at a dose of 75 mg/m2, 800 mg/m^2, and 20 mg/m^2 mitomycin C, respectively.

The incidence of hypomagnesemia was found as 18.6% in this study. The mean onset time of hypomagnesemia was three days (range, 1-6 days). Hypomagne-

Table 1 • The demographic and clinical characteristics of 8 patients with hypomagnesemia.

	Mean (range)
Age (years)	56.1 (48-68)
Body Mass Index (kg/m^2)	26.4 (18.9-34.5)
Comorbidity (number)	
Haemoglobin (g/dl)	10.9 (9.8-13.5)
Creatinine (mg/dl)	0.65 (0.4-0.9)
Blood urea nitrogen (mg/dl)	16.7 (6-20)
Urea (mg/dl)	31.6 (19-43)
Albumin (g/dl)	3.8 (2.3-4.5)
Preoperative ascites (number)	
No ascites	1
<500 ml	7
>500 ml	0
Intensive care unit stay (days)	2 (1-3)
Hospital stay (days)	11 (6-22)

semia developed in five of 32 patients (15.6%) treated with cisplatin, two of 10 patients (20.0%) treated with carboplatin, and one patient treated with mitomycin C. None of the patients had a neurological symptom. Oral magnesium (365 mg) was administered two times a day until the serum magnesium values reach a normal range of 1.6 to 2.5 mg/dL. The magnesium levels returned to normal values after the application of magnesium treatment after a median of 19 days (range, 7-32 days).

The mean onset time of hypopotassemia was three days (range, 1-8 days). Oral potassium (2.17 gr potassium citrate and 2 gr potassium bicarbonate) was administered to one patient once daily for four days. Intravenous potassium (3 gr) was administered to 7 patients once daily until the serum potassium values reach the normal range of 3.5 to 5.1 mmol/L. Additionally, one patient developed hyponatremia (Reference range: 136-145 mmol/L) following interval CRS-HIPEC. Sodium chloride was administered to this patient intravenously. The perioperative parameters of the patients included in the study are shown in Table 2.

The mean length of stay in the intensive care unit (ICU) for patients who developed hypomagnesemia was two days (range, 1-3 days). The mean length of stay in the hospital, excluding ICU stay was 11 days (range, 6-22 days). Pancreatic leakage occurred in one patient who had undergone distal pancreatectomy on postoperative day one and managed conservatively and left adrenal bleeding occurred in one patient. Serum electrolytes were measured daily as part of our routine practice. All of the patients received intravenous chemotherapy within 22 days of surgery.

Discussion

HIPEC is the procedure of delivering heating chemotherapy drugs into the abdominal cavity following CRS. The procedure increases the effect of chemotherapy drugs by multiple mechanisms. Heating at 41-42 °C increases membrane permeability and drug penetration into the cells (7). In line with standard procedure, cisplatin, mitomycin C, or carboplatin was administered during HIPEC in the current study. Recurrence-free and overall survival benefits were observed among the patients who received HIPEC following CRS in some of the previous trials (2, 8). Van Driel et al. in their phase III trial evaluating the role of HIPEC in patients having neoadjuvant chemotherapy demonstrated 3.5 months recurrence-free and 11.8 months overall survival advantage after 90-minute using of cisplatin (100 mg/m^2) (2).

Longer operation time might cause more costs and extra hospital and/or ICU stay (2). Although CRS-HIPEC has positive results for selected patients, many physicians are averse due to its morbidity (8-10). Several intraoperative and postoperative complications, including bleeding, anastomotic leak, respiratory, entero-cutaneous fistula, chemical peritonitis, pneumonia, wound infection, ileus, neutropenia, acute renal impairment, acute pulmonary hypertension, and sclerosing encapsulating peritonitis were reported to be associated with HIPEC in the past literature (11-13). Kim et al. reported that major complications occurred more frequently in patients who had multiple organ resections, longer operation times, and high blood loss during sur-

Table 2 • The perioperative parameters of the patients.

Variable	Number
Antineoplastic agent (n)	
Cisplatin (75 mg/m^2)	5
Carboplatin (800 mg/m^2)	2
Mitomycin C (20 mg/m^2)	1
CRS duration (minutes) (mean (range))	311 (135-670)
Intraoperative fluid replacement (ml)	
Crystalloid	4230
Colloid	625
Intraoperative transfusion of packed red blood cells	Median (range): 1 (0-8) (n=5/8)
Intraoperative transfusion of packed fresh frozen plasma	Median (range): 2.5 (1-8) (n=8/8)
Intraoperative albumin replacement (ml)	Median (range): 50 (0-400) (n=4/8)
Arterial blood gas (pH) (mean)	
At the beginning of the CRS	7.41
At the end of the CRS	7.36
At the end of the HIPEC	7.33
Intraoperative urine output (ml/hour) (mean)	86.4

Table 3 • The surgical procedures performed during cytoreductive surgery

	Case	Age (years)	NCT	Surgical procedures	Hypo-Mg	Hypo-K	Hypo-Na	Peri-operative complication	Post-operative complication
Newly diagnosed	1	64	-	Standard surgery†, diaphragmatic stripping, pelvic peritonectomy, liver metastasectomy.	+	+	+	-	-
	2	55	3 CCPPPT	Standard surgery†, recto-sigmoidectomy, partial ileum resection, liver metastasectomy, celiac lymphadenectomy.	+	+	-	-	-
	3	68	4 CCPPPT	Standard surgery†, low anterior resection, cholecystectomy, peritonectomy, liver metastasectomy, diaphragmatic stripping, distal pancreatectomy, splenectomy.	+	+	-	-	-
	4	51	6 CCPPPT	Standard surgery†, total colectomy, terminal ileum resection, subtotal gastrectomy, total peritonectomy, distal pancreatectomy, splenectomy, diaphragmatic stripping.	+	+	-	-	Pancreatic leakage
	5	47	3 CCPPPT	Standard surgery†, low anterior resection, cholecystectomy, diaphragmatic stripping, total peritonectomy, splenectomy, liver metastasectomy.	+	+	-	Left adrenal bleeding	-
	6	65	-	Gastric antrum resection, bilateral pelvic-paraaortic lymphadenectomy, omentectomy, liver metastasectomy, appendectomy.	+	+	-	-	-
	7	51	-	Colectomy, cholecystectomy, diaphragmatic stripping, peritonectomy, left ureter excision, partial bladder excision, liver metastasectomy, splenectomy.	+	+	-	-	-
	8	48	-	Cholecystectomy, cardio-phrenic lymphadenectomy, resection of pancreatic capsule, metastasectomy of abdominal wall.	+	+	-	-	-

†Standard surgery includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic-paraaortic lymphadenectomy, omentectomy, and appendectomy. NCT: Neoadjuvant chemotherapy; CCPPPT: cycles of carboplatin plus paclitaxel; Hypo-Mg: Hypomagnesemia; Hypo-K: Hypopotassemia; Hypo-Na: Hyponatremia.

gery (14). On the other hand, in a retrospective cohort study of 1822 patients, Foster et al. demonstrated that CRS-HIPEC was safe compared with similar-risk oncologic procedures (right lobe hepatectomy, trisegmental hepatectomy, pancreaticoduodenectomy (Whipple), and esophagectomy) in terms of perioperative and 30-day postoperative morbidity and mortality rates (15). Although rare, the potential for pulmonary toxicity of mitomycin C must be considered (16). Additionally, Zajonz et al. reported acute pulmonary hypertension after HIPEC with oxaliplatin and 5-fluorouracil (13).

Cisplatin is one of the most commonly used chemotherapeutic agents in HIPEC, and cisplatin-related nephrotoxicity is a well-recognized complication. Platinum-based antineoplastic drugs can cause severe renal tubular damage (17). Renal toxicity has been noted in 28 to 36% of patients treated with a single dose of intravenous cisplatin (4). All platinum-based antineoplastic drugs have the potential for AKI, although the peritoneal barrier blocks the passing of the drugs into the systemic circulation during HIPEC and potentially limits the major side effect. Dagel et al. demonstrated that the incidence of cisplatin nephrotoxicity that was manifested as AKI was 31.2% following HIPEC (3). Mitomycin C also has a potential risk for renal injury (18). Perioperative careful fluid management aids in reducing acute renal impairment rates.

The mean serum albumin level was 4.2 g/dl before the operation. Albumin is often given to patients with a low albumin level during and after CRS-HIPEC because it has been shown that chemotherapeutic drug binding to albumin may attenuate its renal injury (19). Furthermore, approximately 30% of magnesium is bound to albumin; hypoalbuminemic states may lead to low magnesium values (20).

In this study, we detected that HIPEC was a risk factor for hypomagnesemia. The current study showed that perioperative parameters were not related to hypomagnesemia risk. Hypomagnesemia can develop even in the absence of a decline in the glomerular filtration rate (GFR) (21). In a retrospective study, the incidence of hypomagnesemia was reported as 30.1% after HIPEC (4). Six of eight patients included this study underwent partial gastric resection, intestinal resection or/and colectomy. Hypomagnesemia may develop secondary to insufficient dietary intake depended on the surgical resection of parts of the gastrointestinal tract and/or a defect in magnesium reabsorption (22). Kuhar et al found an incidence of hypomagnesemia of 20% in patients who underwent four cycles of platin-based induction chemotherapy (23). The incidence of cisplatin-induced hypomagnesemia in 32 cervical cancer patients receiving cisplatin alone was 56.3% (24). At any point during chemotherapy, Hodgkinson et al. found an incidence of hypomagnesemia of 43% and showed a significant association between dose, frequency, and a number of cycles given, and the degree of hypomagnesemia (25). In addition, Crook et al. reported that hypopotassemia was found in 25% of patients with hypomagnesemia (26).

Magnesium is known to be a critical cofactor in cellular repair and membrane transport (27). Lajer et al. indicated a substantial additive effect of magnesium-depletion on cisplatin-induced renal toxicity (28). Liu et al. found that a greater frequency of hypomagnesemia episodes during the treatment with carboplatin was significantly associated with shorter survival independent of completeness of tumor reduction and stage (29). Limitations of this study include its retrospective design, small sample size, and heterogeneous study group.

In conclusion, multiple morbidities, including hypomagnesemia, must be considered in the management of patients undergoing CRS-HIPEC. Hypomagnesemia is a potential complication associated with CRS-HIPEC, and it cannot be predicted preoperatively. Albumin replacement should be considered in patients with low preoperative serum albumin level in order to minimize the toxicity of chemotherapeutic drugs. Routine measurement of magnesium levels in the preoperative and postoperative period might be useful for the patients who will receive HIPEC to rule out hypomagnesemia.

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