

# Post-Operative Femoral Neuropathy in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC)

E. Mor\*, Dux J, Schtrechman G, Ben-Yaacov A, Zippel D, Hazzan D, Shapiro R and Nissan A

Department of General and Oncological Surgery-Surgery C, The Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan,

Affiliated with Sackler School of Medicine, Tel Aviv University

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\*Corresponding author: E. Mor, Department of General and Oncological Surgery-Surgery C, The Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan, Tel.No: +972-3-530-2714, Fax: +972-3-5341562, Email: [eyal.mor@sheba.health.gov.il](mailto:eyal.mor@sheba.health.gov.il)

## Abstract

**Background:** Post-Operative Femoral Neuropathy (POFN) is a rare complication associated with various abdominal and pelvic surgical procedures. Patients present with a combined motor and sensory deficit of the lower extremities. This neuropathy resolves with none or minimal residual deficit after physiotherapy and rehabilitation. The aim of this study is to describe and compare by matched case - control method four cases of postoperative femoral nerve injury in patients undergoing Cytoreductive Surgery (CRS) and Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC).

**Methods:** This is a retrospective analysis of a prospectively maintained database including all patients who underwent CRS+HIPEC between the years 2007-2016 for the treatment of peritoneal surface malignancies (n=290). Four patients with POFN were identified and compared to the entire cohort by age, gender, and type of primary tumor.

We used a match case - control method to identify possible factors that may be associated with this syndrome. A 3 to 1 match was performed, a total of 12 patients were selected to the matched control group using the following parameters: Type of primary diagnosis (underlying disease), gender, age and type of chemotherapy regimen used for HIPEC.

**Results:** Of the 290 patients reviewed, only 4 cases (1.4%) patients with femoral neuropathy were identified. There were no significant differences between the control group and the affected group in the BMI (p value-0.9), OR time (p value-0.3) and estimated blood loss (p value-0.8). PCI was higher in the POFN compared to the control group (19±11.6 vs 8±9, respectively, p= 0.07) All POFN patients were followed up for a period of 12 months with a complete or near complete resolution of symptoms.

**Conclusions:** POFN is a rare syndrome of combined motor and sensory deficit associated with complex pelvic operations. High PCI reflecting higher disease burden may increase the risk for POFN. All cases of femoral neuropathy showed complete or near complete resolution of the symptoms after rehabilitation therapy.

## Introduction

Post-operative femoral neuropathy is a rare condition associated with a variety of surgical procedures including colo-rectal resections, inguinal hernia repair, hysterectomy, cystectomy and hip replacement [2-5,8,9,11,14,18]. The underlying mechanism is yet unknown. It is likely to assume that POFN is associated with compression of the nerve by surgical instruments such as a self-retaining retractor or direct injury to the genito-femoral nerve [3,4,8,11,19,22].

Cytoreductive Surgery (CRS) and Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) is gaining wide acceptance as the procedure of choice for various peritoneal surface malignancies. This complex procedure involves peritonectomy procedures and visceral organ resections followed by administration of HIPEC [1]. This combined procedure lasts 6-12 hours with a self-retaining retractor applying pressure on abdominal wall tissues.

We describe four cases of POFN in patients who underwent CRS+HIPEC. The symptoms included sensory deficit such as pain and paresthesia of the proximal part of the lower extremity, and a motor deficit including weakness of the ileopsoas and the quadriceps muscles.

The aim of the study was to identify possible risk factors for POFN in patients undergoing CRS+HIPEC.

## Methods

A prospective database containing the records of patients who underwent CRS + HIPEC between the years 2007-2016 was reviewed. All patients were operated by the same surgical team using the same technique. Briefly, Patients had combined general and epidural anesthesia, positioned in the lithotomy position and had a midline xyphoid to pubis incision while resecting

previous surgical scar tissue. Following initial inspection of the abdomen and pelvis, a self-retaining Buckwalter retractor was placed. All HIPEC procedures following cytoreductive surgery were performed according to established protocols using the closed abdomen technique. Wide laparotomy with resection of all previous surgical scars and primary survey for assessment of the operative PCI was performed. Any area of visible metastatic disease was resected and peritonectomy procedures were performed as described by Sugarbaker [1]. At the end of the cytoreduction procedure, completeness of cytoreduction was assessed. HIPEC was added only in cases of complete CRS with a completeness of cytoreduction score (CC) of 0 or 1. HIPEC was done using the Performer HTTM system, (Rand-biotech, Medolla, Italy). After completion of cytoreduction, inflow and outflow catheters were inserted: two inflow catheters on the liver surface, three outflow drains one in each sub-phrenic space and one in the pelvis. Two thermometers and a pressure detector were also inserted. After the catheters were inserted, the fascia was closed with interrupted PDS 1 sutures and subsequent skin closure. The abdomen was perfused with 3000 mL of 0.9% NaCl solution or D5W depending on the drug protocol used during HIPEC. The solution was heated to 44°C at the inflow with a mean temperature of 42°C.

**The chemotherapy agents used were**

1. In cases of colorectal cancer, Mitomycin C (MMC) intra-peritoneal 20mg/m<sup>2</sup> for 90 minutes at a temperature of 42C combined with intravenous 400mg/m<sup>2</sup> Fluorouracil(5FU) and 20mg/m<sup>2</sup> Leucovorin.
2. In cases of low grade mucinous neoplasm of the appendix, single agent MMC intra-peritoneal 20mg/m<sup>2</sup> for 90 minutes at a temperature of 42°C.
3. In cases of ovarian carcinoma, intra-peritoneal Cisplatinum at 75mg/m<sup>2</sup> combined with Doxorubicin at 15mg/m<sup>2</sup> of for 60 minutes at a temperature of 42°C.

Out of 290 patients who underwent CRS+HIPEC at our institution, 4 cases of POFN were identified. We used a match case - control method to identify possible factors that may be associated with this syndrome. A 3 to 1 match was performed, a total of 12 patients were selected to the matched control group

using the following parameters: Type of primary diagnosis (underlying disease), gender, age and type of chemotherapy regimen used for HIPEC.

The following parameters were compared between the POFN patients (n=4) and the control group (n=12): Body Mass Index (BMI), duration of surgery, Peritoneal Cancer Index (PCI) and Estimated Blood Lost (EBL), in order to identify a potential relationship to POFN.

All study patients were followed for at least 12 months with a full neurological assessment.

**Statistics:** Summary statistics were performed using established methods. All results are expressed by mean + SD unless otherwise indicated in the text. Difference between continuous variables was tested using Student’s -t test and among categorical variables using Chi square test or Fisher exact test according to sample size.

All statistical analysis was performed using SPSS®, statistical package, IBM, Chicago, USA.

**Results**

There were four patients out of 290 CRS+HIPEC procedures diagnosed with POFN (1.4%). In the affected group (AG) there were two patients with low grade mucinous neoplasm of the appendix, one with ovarian carcinoma and one patient with adenocarcinoma of the cecum. There were three females and one male patient, Median age was 51.5 years (range 35-61). In all four cases a Self-retaining retractor was used throughout the procedure. There were three males and nine female patients in the control group (CG) with a median age of 53 years (range 44-72). In all cases of the control group, a self-retaining retractor was used throughout the procedure (table 1).

The mean BMI was 22.72±3.44 in the AG and 22. 2±4.9 in the CG (p=0.97). The mean EBL was 500ml ±346 and 458ml ±394 in the AG and CG groups, respectively (p=0.85). Operating time was 5.6 hours ±2.92 and 4.5 hours ±2.04 for the AG and CG groups respectively, (p=0.36). The mean PCI was 19 ±11.6 and 8±9 for the AG in the CG, respectively (p=0.07), table 2. All four patients in AG had a low BMI (19-27), being more than 4 hours in a lithotomy position, and a high PCI (<15) with pelvic disease.

**Table 1:** Comparison of studied parameters between the two groups.

parameters	POFN	Control	P value (t-test)
BMI (mean±SD)	22.72±3.44	22.2±4.9	0.97
Mean ± SD EBL (ml)	500±346	458±394	0.85
Mean operative time mean±SD (hours)	5.6±2.2	4.5±2.04	0.36
PCI score (mean±SD)	19±11.65	8±9	0.071

**Table 2:**Description of the affected group

N	Age	Gender	Primary tumor	Past surgical history	Previous chemotherapy	Pelvic peritonectomy	BMI	PCI	OR Time (hours)	POD of Dx	MD	SD	RD
1	61	M	Adeno ca of appendix		none	YES	21	33	8	5	IP and Quad 3/5	0	1 - 4/5 both
2	46	F	Ovarian Cancer	Hysterectomy BSO	Carboplatin taxol	YES	24	7	3	2	IP 4/5 Quad 4/5	1	0
3	35	F	Low grade mucinous of appendix		none	YES	19	22	7	4	IP 4/5 Quad 0/5 TA 4/5	1	0
4	57	F	Adenoca of cecum	Rt Hemicolectomy	FOLFOX	YES	26	14	4.5	3	IP 2/5 Quad 1/5	1	0

PSH – past surgical history, POT – past oncological therapy, ORT – Operating time, POD – post operation day. MD - Motor deficits, SD- Sensory Deficit, RD - Residual Deficit (after 6 month).

All patients participating in the study were followed for at least 12 months with complete resolution of all symptoms in all but one patient. This patient, a 61 year old male patient with mucinous adenocarcinoma of the vermiform appendix (Pseudomyxoma Peritonei) with high PCI of 33, suffered POFN in both lower extremities. After intense in-patient rehabilitation followed by ambulatory rehabilitation, all motor deficits returned to baseline.

In all four patients with POFN, a full Neurological examination and EMG were performed. Iliopsoas muscle 2/5 motor deficit was observed in one patient, 3/5 in one patient and 4/5 in two. Motor deficit of the quadriceps muscle of 0/5 was measured in one patient, 1/5 in one, 3/5 in one and 4/5 in one patient. A 4/5 motor deficit of the anterior tibialis was measured in one patient. Sensory deficit in the appropriate distribution was recorded in 3/4 POFN patients.

After a POFN was diagnosed, a rehabilitation program was performed by rehabilitation specialists and physiotherapists. The rehabilitation started in-hospital in parallel with recovery from surgery and continued on an outpatient basis in 3/4 POFN patients until resolution of all symptoms was observed. One patient was transferred as in-patient to a rehabilitation facility until significant improvement was observed. He then continued physiotherapy on ambulatory basis until resolution of all symptoms except for a residual motor deficit of the iliopsoas muscle of 4/5. One year following discharge from the hospital, all four patients are fully active without significant neurological disease and cancer-free.

## Discussion

The femoral nerve originating from the second, third and fourth lumbar roots to form the lunar plexus .It passes along the lateral border of the psoas muscle and enters the thigh. It branches in the pelvis to supply the iliacus and psoas muscles, while the rest of the nerve split into anterior and posterior rami. The anterior ramus supplies the pectinous and sartorius muscles and carries sensation from the anteromedial surface of the thigh, while the posterior ramus enervates motor function of the

quadriceps and cutaneous-sensory innervation of the medial side of the leg from the knee to the internal malleolus [7].

Injury to the femoral nerve presents as a combined motor and sensory deficit. The motor deficit is characterized by weakness of the extensor muscles of the lower leg, wasting of the quadriceps muscle and failure of fixation of the knee. Patients complain of gait disturbances and difficulty in ascending stairs. The sensory deficit is characterized by hypoesthesia or paresthesia of the anterior part of the thigh and the medial aspect of the lower leg [3].

POFN is a rare complication associated with various abdominal and gynecological surgical procedures. POFN was first described in 1860. Since then, multiple reports published in the medical literature describe it as a temporary motor and sensory neural deficit of the lower extremity, resolving with appropriate physiotherapy [3,13,17].

The exact mechanism of injury leading to POFN is yet unknown. Goldman, et al. suggested a mechanism of direct compression of the femoral nerve by a self-retaining retractor such as Bookwalter of Balfour [3]. The compression applied by the blade of the retractor for a long period of time may cause femoral nerve injury. They reviewed 3786 patients who underwent abdominal surgery and showed an a risk of 7.4% for POFN with the use of a self-retaining retractor compared to abdominal operations of the same type and duration performed without a self-retaining retractor [15,16]. In a long midline incision reaching the pubic bone, the self-retaining retractor may apply pressure on the femoral nerve at the point where it ascends from the retroperitoneum toward the femoral canal. In cases where Pfannenstiel incision is used, a lateral extension permits a more lateral localization of the retractor and may increase the risk for the neuropathy due to compression of the femoral nerve in the same location.

The position of the patient may also be an important risk factor for POFN. Hakin and Katiji suggested that in the lithotomy position the femoral nerve may be stretched due to an excessive hip abduction and external rotation [6].

Other factors such as body stature and weight can contribute to the formation of POFN. Lean patients with a BMI of less than 20 showed increased risk for POFN while being in the lithotomy position for more than 4 hours [13,14].

In our study, all four patients in AG had a low BMI (19-27), being more than 4 hours in a lithotomy position, and a high PCI (<15) with pelvic disease. It is also important to notice that since all patients had significant volume of disease, pre-operative BMI is higher than the actual BMI suggesting leaner body mass. In patients with pseudomyxoma peritonei, arising from a low grade mucinous neoplasm of the vermiform appendix, the high volume of mucin accumulating over a long period of time is associated with thinner and more flaccid abdominal wall. Therefore, pre-operative BMI may not correlate with the risk of POFN. Operating time did not correlate with the presence of POFN but it is important to notice that all four POFN patients were in a lithotomy position for more than 4 hours, a known risk factor. Estimated blood loss correlates with complexity of the surgical procedure, was not a risk factor for POFN. Peritoneal Cancer reflects the burden of peritoneal disease. A PCI higher than 10 is considered high. The burden of peritoneal disease reflects directly on the duration and complexity of the surgical procedure. PCI was also shown to correlate with post-operative morbidity [10,12]. All four patients underwent pelvic peritonectomy which by itself may be associated with a direct damage to the femoral nerve. All 12 patients had a mean Core body temperature of 42°C, with the use of various Chemotherapy protocol according to the primary diagnosis. Hyperthermia or Chemotherapy regimens did not correlate as risk factors for POFN.

Goldman, et al. showed that 94 % of the patients with postoperative POFN had a complete resolution of all symptoms and signs of POFN [3]. All other 6 % of patients in their study experienced mild residual symptoms. In our four patients, immediate and intense rehabilitation program was initiated in the hospital and continued until patients were fully active and without symptoms. The immediate diagnosis and early rehabilitation may have contributed to the successful outcome.

It is difficult to identify risk factors for POFN in such a small group of patients. However, in order to prevent future incidence of POFN, we have modified the retraction method during CRS+HIPEC procedures. We initially apply all four blades of the Bookwalter retractor. Following inspection of the abdomen and pelvis, the pelvic blades are released until all other parts of the abdomen are cleared from disease. Shortly before pelvic peritonectomy is commenced, the pelvic blades are re-positioned. This modification shortens the duration of pressure on the femoral nerve and as a result, there was no case of POFN in over 100 consecutive cases.

## Conclusion

Post-operative femoral neuropathy is a rare complication of pelvic surgery with a combined motor and sensory neurological deficit. Complete or near complete resolution was observed

after early and aggressive rehabilitation program was initiated. Prevention of this complication can be obtained by careful attention of patient positioning and retractor application during prolonged abdominal and pelvic surgery.

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